CANCER RESEARCH

VOLUME 8
NUMBER 2
FEBRUARY, 1948

A MONTHLY JOURNAL
REPORTING CANCER RESEARCH

CONTENTS

HODGKIN'S DISEASE - (Part II)
1832-1947

HERMAN A. HOSTER, M.D.
Professor and Coordinator of Oncology
The Ohio State University College of Medicine, Columbus, Ohio
and
MARY B. DRATMAN, M.D.
Graduate Research Student in Pathology
The Women's Medical College of Pennsylvania, Philadelphia, Pennsylvania

edited by

LLOYD F. CRAVER, M.D.
Chief of Medicine, Memorial Hospital
New York, New York
and
HARRY A. ROLNICK, Ph.D.
Secretary of The Hodgkin's Disease Research Foundation, Inc.
New York, New York

THE OFFICIAL ORGAN OF THE
AMERICAN ASSOCIATION FOR CANCER RESEARCH, INC.

CANCER RESEARCH

This journal is sponsored by The American Association for Cancer Research, Inc.; The Anna Fuller Fund; Cancer Research Division, Donner Foundation, Incorporated; The Jane Coffin Childs Memorial Fund for Medical Research; and The Elsa U. Pardee Foundation.

Published by Cancer Research Division, Donner Foundation, Incorporated
Publication Office, 317 Maynard Street, Ann Arbor, Michigan

The annual subscription rates for one volume are: To members of the American Association for Cancer Research, Inc., $5.00; to others and to libraries, institutions, and organizations. domestic, $7.00; Canadian, $7.50; foreign, $8.00. Single copies, $1.00. Business communications, remittances, and subscriptions should be addressed to Dr. Theodore P. Eberhard, Business Manager, Jefferson Hospital, 10th and Sansom Streets, Philadelphia 7, Pa.

Entered as second class matter December 16, 1946, at the Post Office at New Haven, Conn., under the Act of March 3, 1879. Application pending transfer to Ann Arbor, Mich.

CANCER RESEARCH
A MONTHLY JOURNAL OF ARTICLES AND ABSTRACTS REPORTING CANCER RESEARCH

VOLUME 8 FEBRUARY, 1948 NUMBER 2

HODGKIN'S DISEASE - (Part II)
1832-1947

HERMAN A. HOSTER, M.D.
Professor and Coordinator of Oncology
The Ohio State University College of Medicine, Columbus, Ohio
and
MARY B. DRATMAN, M.D.
Graduate Research Student in Pathology
The Women's Medical College of Pennsylvania, Philadelphia, Pennsylvania

edited by

LLOYD F. CRAVER, M.D.
Chief of Medicine, Memorial Hospital
New York, New York
and
HARRY A. ROLNICK, Ph.D.
Secretary of The Hodgkin's Disease Research Foundation, Inc.
New York, New York

MacMahon and Stalker each report what they consider to be spontaneous Hodgkin's disease in the dog. Since these cases are rare, the descriptions are given in detail.

MacMahon (345): Before death, the dog developed a firm swelling in a cervical node. The skin was somewhat adherent to this node, and there was a small abrasion of the skin. Autopsy revealed massive enlargement of the cervical lymph nodes. They were adherent to the surrounding tissues and the individual nodes could not be defined. Some areas were soft, some fibrous, while others were "slightly caseous, suggesting areas of necrosis." MacMahon reported that microscopic examination revealed the histologic changes of Hodgkin's disease with invasion of the surrounding tissue. Giant cells resembling Sternberg-Reed cells with two to four nuclei were present. "Atypical" features included absence of eosinophils and the presence of large, thin-walled vessels. No other focus with the exception of that in the right side of the neck was found. An attempt was made to isolate tubercle bacilli without success. Stalker, Schlotthauer and Feldman (484): A moribund dog with gastrointestinal symptoms was killed. Autopsy revealed ascites and a grey nodular tumor involving the pancreas and peripancreatic tissues. All the mesenteric lymph nodes were enlarged and firm. Miliary nodules were distributed throughout the liver and spleen and apices of both lungs. The peribronchial lymph nodes were enlarged and firm. "Grossly, all the involved nodes looked like Hodgkin's disease." Some foci in the liver were cellular, some fibrotic; no necrosis was seen. Microscopic section revealed many eosinophils, reticular (or epithelioid cells), lymphocytes and plasma cells. Multinucleated cells resembling those described by Sternberg, Reed and others were present. "The more cellular areas contained a definite delicate reticular framework which contained many vascular channels. Fibrosis seemed to originate in the central portions of the lesions while the peripheral portions remained cellular and progressive. A brownish-black to brownish-yellow granular pigment contained within unidentified cells was present throughout most of the lesions in the liver." In the lung an occasional giant cell

resembling the Langhan's type was seen. The spleen was hyperplastic and contained gross "Hodgkin's lesions." The abdominal mass was very fibrotic and appeared to be a chronic infectious type of lesion. The nodes were fibrotic and contained "Sternberg-Reed cells"; there was no evidence that the process had extended beyond the capsule. The bone marrow contained many myelocytes, particularly the eosinophilic variety.

Stalker and associates conclude that the lesions were due to Hodgkin's disease and that the abdominal tumor, though failing to contain the typical cells, was probably of the same origin and that the picture was distorted by secondary infection.

Medlar and Sasano (376) reported Hodgkin's disease in a rabbit. A hybrid doe was given a single intravenous injection of heat-killed Brucella abortus in February 1932. There was a complete loss of hair and marked emaciation in 1933, "but this condition has been recorded in other animals and *per se* has no relation to the injection." The animal fully recovered and was in good health thereafter; it died in 1936. At autopsy, grey spots were found in the lung which proved to be foci of fungus disease. The right and left ventricles and both auricles were involved in the process. Scattered throughout the liver were firm greyish spots like tubercles. The spleen, both adrenals, the distal part of the appendix, the mesentery, the pancreas and the left ureter were enlarged, nodular and probably infiltrated by a retroperitoneal tumor. There were enlarged lymph nodes in the mesentery and about the pyloric end of the stomach. The mediastinal lymph nodes were more prominent than usual. The histologic picture observed in the lymph nodes, spleen, liver, heart, adrenals and retroperitoneal tissue "in some areas, strongly resembled Hodgkin's disease and in others gave the picture of a rapidly growing lymphosarcoma." The bone marrow was hyperplastic with an increase in megakaryocytes. Postmortem examination of heart blood revealed 72% polymorphonuclear leukocytes, 8% lymphocytes and 20% monocytes. The left ureter contained areas of erythro-, leuko- and megakaryogenesis. Small areas of erythropoiesis were seen in the lymph nodes, spleen and appendix. Other rabbits which received the Brucella injection at the same time developed no lesions similar to those described by the authors.

Forbus and Davis describe a reticuloendothelial syndrome in 7 swine that they considered to bear "an extraordinary resemblance to Hodgkin's disease if it is actually not that disease" (160). In general, the lesions involved the lymph nodes, spleen, liver, bone marrow and kidney. The lesions were densely scarred granulomas on gross appearance and microscopic examination revealed a pleomorphic cellular aggregate with eosinophils, plasma cells, epithelioid cells, reticulum cells, monocytes, lymphocytes, polymorphonuclear leukocytes and giant cells which in some animals were indistinguishable from Sternberg-Reed cells. Dense fibrous tissue reactions were almost constant. The description of the deforming fibrosis of the hog livers is reminiscent of the case of Hodgkin's disease with cirrhosis described by Steiner (488).

6. TRANSMISSION EXPERIMENTS

Transmission to animals.—Attempts to produce animal infection have been frequent, repeated and exhaustive and thus far unsuccessful with the exception of Delbet's report (126) concerning a single isolated case of Hodgkin's disease in the dog.

The observations of Longcope (335), made during transmission experiments, are interesting but inconclusive. Large doses of emulsions of lymph nodes obtained at operation were injected repeatedly under the skin of the chest and upper arm in a group of monkeys. In one instance, small pieces of node were used instead of emulsions, and later in the course of the experiments the emulsions were fed in addition to being injected subcutaneously. All nodes were cultured before use and no bacterial growth was obtained. One month after inoculation, the monkeys began to exhibit "definite glandular enlargement in the axillary, inguinal and cervical glands." The nodes were excised 1 week later; they contained "extensive hyperplasia of lymphoid elements." The lymph sinuses were "filled with cells and, except for the ones about the hilus, were almost completely obliterated. There was some proliferation of the reticulum in the peripheral sinuses. Many of the large, pale cells showed karyokinetic figures. There were quite a number of large epithelioid cells, some almost of giant size, with single pale nuclei. Only one or two multinucleated giant cells were seen. Occasional loose clumps of plasma cells were present." After the feeding of emulsion was begun, a marked submaxillary glandular swelling was noted. In a few weeks, however, the swellings disappeared, and the monkeys recovered in spite of repeated injections and feedings of lymph nodes.

Cunningham and McAlpin (116) investigated 4 monkeys with the following results:

Monkey No. 1.—A Hodgkin's node was transplanted into the retroperitoneal region and into the spleen. At autopsy several months later nothing was found with the exception of fibrosis of the manipulated portion of the spleen.

Monkey No. 2.—A node was transplanted into the retroperitoneal tissue. No clinical evidence of disease became apparent and at autopsy several months later no abnormal findings were noted.

Chimpanzees No. 1 and No. 2.—Hodgkin's nodes were transplanted into the deep cervical fascia of 2 animals. They were observed for 2 years without clinical evidence of disease. Following release from their cages, both contracted tuberculosis and died. Since these animals are susceptible to tuberculosis, the authors feel certain that the infection was accidental and that its onset had nothing whatever to do with the node transplants. Cunningham and McAlpin conclude that there is "no evidence that Hodgkin's disease was produced in any of these animals."

Stewart and Dobson (498), in 1924, also attempted production of the disease in monkeys by means of lymph node transplants. Five monkeys were used; laporatomy was performed and small chips of fresh Hodgkin's nodes were implanted in some of the mesenteric lymph nodes.

Monkey No. 1 (female Macacus rhesus).—A node from a case with marked eosinophilia was transplanted as described above. The animal was killed at the end of 19 weeks. A number of mesenteric nodes were found to be enlarged. In 1, an abscess cavity lined by foreign-body giant cells, lymphocytes and plasma cells was found. The other nodes contained large lymph follicles and large and active germinal centers. The malpighian bodies of the spleen were very large and hyperplastic germinal centers were observed.

Monkey No. 2 (male Macacus rhesus).—A node was transplanted from the case used as donor for monkey No. 1. The animal had to be killed on the tenth day because of a staphylococcic infection of the wound. No changes suggestive of Hodgkin's disease were seen in the implanted areas.

Monkey No. 3 (male Macacus rhesus).—A node was transplanted from the case used as donor for No. 1 and No. 2. A thick emulsion of the Hodgkin's tissue was injected into the spleen and abdominal lymph nodes. The animal remained well for one year at which time laporotomy revealed adhesions about the spleen and a small abscess cavity containing a nematode at the site of the lymph node injections. The animal was killed after 2 years; no changes found at autopsy.

Monkey No. 4 (Bonnet monkey).—Tissues from a case of Hodgkin's disease without eosinophilia were emulsified and injected or implanted as chips into the spleen and abdominal lymph nodes. Laporotomy was performed 4½ months later, the spleen was excised and more Hodgkin's tissue introduced; no gross lesions were observed at operation. The animal was killed 32 months later and no pathologic changes were noted.

Monkey No. 5 (Macacus rhesus).—No pathologic changes were observed in this uninoculated control animal.

Chevallier and Bernard (81) report the occurrence of a syndrome of cachexia and weight loss in guinea pigs following subcutaneous implantation of Hodgkin's nodes. Although there was no adenopathy, the lymph nodes were characteristic of "Hodgkin's disease on microscopic examination." H. L. Stewart (496) inoculated rabbits with cotton plugs containing crushed Hodgkin's nodes and found no lesions at autopsy. He also gave India ink to guinea pigs "to block the reticuloendothelial system" and then inoculated them with nodes from 5 cases of Hodgkin's disease without successful reproduction of the lesions. Jianu and Netta (274) report the appearance of sarcoma in a rabbit at the level of the graft following the implantation of Hodgkin's tissue. The authors discuss two possible interpretations of this finding: (a) Coincidence, in view of the frequency of spontaneous malignant tumors in rabbits, with occurrence of the sarcoma at the site of the implant because of the irritation of the foreign body graft. (b) Sarcomatous evolution of the lymphogranulomatous graft.

Chapman (76) felt that transmission to dogs might prove successful since "the disease had been described in those animals." Therefore "using the method of Drinker, the paw lymphatic of 3 large shepherd dogs was canulated and fresh saline emulsions of diseased lymph nodes were injected. In two days the injections were repeated, so that in all, the material from five patients with Hodgkin's disease was used." After this the dogs were observed clinically from 7 months to 3 years and then killed. On necropsy of each dog, no evidence of disease resembling Hodgkin's could be found.

Diseased splenic and lymph node tissues from patients with Hodgkin's disease and control tissues from 8 patients with other lymphomas were investigated by Steiner (486). This author used guinea pigs, chickens, rabbits, dogs and mice as experimental animals. "No evidence was found that the diseased human tissues were transplantable or that they were capable of producing, in animals, lesions of a similar histological structure."

Hoster, Doan and Schumacher (249) injected 66 guinea pigs subcutaneously, 30 leghorn chickens and 8 rabbits intravenously with thick emulsions of Hodgkin's tissue and used lymphatic tissue emulsions from other diseases as controls. All animals were autopsied at death or 8 months after inocula-

tion. "In one of the guinea pigs inoculated with tissue obtained from a patient with Hodgkin's sarcoma, there was found at autopsy, eight months after inoculation the typical macroscopic appearance of advanced Hodgkin's disease of the human liver in miniature. Microscopically, however, the lesion appeared to be fibrous rather than granulomatous and no reticulum cell hyperplasia was present." No other animals developed this lesion or any others of significance.

After 6 years of experimentation, Twort (514) reported that "animal injection of all types by practically every conceivable route gave no infection even remotely resembling Hodgkin's disease." Occasional inflammatory nodules in guinea pigs at the site of subcutaneous injection were reported both by Twort and Gordon (205, 514).

The intracerebral inoculation of Hodgkin's lymph node emulsions will be discussed under the section devoted to viruses.

Wachsmuth (534) found the changes in Hodgkin's nodes transplanted to animals to be the same as those occurring in normal nodes transplanted to animals. There is early central necrosis followed by cellular infiltration and proliferation of the connective tissue with complete disappearance of the architecture.

Inoculation experiments using material other than diseased nodes have been carried out in an attempt to reproduce the disease in animals. Intraperitoneal injection of blood from patients with active Hodgkin's disease into guinea pigs produced enlargement, congestion and hemorrhage of liver, spleen, kidneys and adrenals (Loeper and Lemaire cited by Wallhauser [538]). Loeper and Lemaire observed intense dilatation of the portal vessels of the liver with numerous necrotic zones often surrounded by cellular accumulations of macrophages and polymorphonuclear leukocytes. Many of the macrophages were filled with acidophilic granules. An animal injected with blood from an active Hodgkin's patient developed splenic nodules filled with sterile caseous pus; at the periphery of the spleen there was a cellular infiltration of eosinophils and multinucleated macrophages similar to Sternberg-Reed cells. The liver and the spleen were enormous and adherent. The resulting lesions were not typical of Hodgkin's disease but were not produced by the blood of controls. Loeper and Lemaire injected urine from patients with active Hodgkin's disease subcutaneously into guinea pigs. The animals died 10 to 12 days later with lesions identical with those produced by blood injection.

It may be pertinent to recall the reaction in guinea pigs observed by Miller and Turner (383) following the injection of urine extract from patients with Hodgkin's disease: enlarged lymph nodes, reticulum cell hyperplasia with many eosinophils and beginning pleomorphism, numerous mitotic figures and giant cells and changes in the kidney.

Transmission to animal embryos.—Hoster and Bechtel (250) studying the effect of explants of Hodgkin's and control tissues on the chorioallantoic membrane and embryo of the fertilized chicken egg concluded that: (a) embryo mortality following exposure of the chorioallantoic membrane to Hodgkin's tissue grafts was in excess of that encountered following exposure to carcinoma, sarcoma, and nonspecific adenitis explants, (b) the mortality of subsequent egg passages following the initial exposure to Hodgkin's tissue did not differ from that observed in the case of cancer, sarcoma, and nonspecific adenitis and (c) the Hodgkin's "graft" does not become vascularized as in the case of carcinoma; and if the embryo survives, the graft often becomes smaller and disappears.

Karnofsky, Parisette, Patterson and Jacquez (285) studying the behavior and growth of a variety of tumors of virus and presumably nonvirus origin on the chorioallantoic membrane of the fertilized chicken egg state that most of the human tumors investigated by them with the exception of a case of anaplastic carcinoma of the lung have not been successfully maintained on the chicken membrane. Lymph nodes and tumors of lymphatic origin frequently induce the formation of an edematous disc around the explant. Hodgkin's disease tissue usually induces a "singularly massive reaction" in the membrane around the explant, and in some instances edematous chick embryos were found. The edematous embryos were found only in eggs bearing Hodgkin's tissue and all attempts tc transmit the effect failed.

Transmission to man.—Rare instances of transmission of Hodgkin's disease from man to man have been reported. One concerns an assistant "who helped to plug the nose and also to examine the urine and feces of a patient who was suffering from acute Hodgkin's disease" and who soon afterwards contracted the same disease and died a month after the time of the alleged contact (396, quoting Obratzow). The second report describes the accidental inoculation of Hodgkin's tissue into the finger of a surgeon. A few weeks later he developed remittent fever and sweats; 2 days after the appearance of these symptoms his axillary nodes enlarged and biopsy revealed Hodgkin's disease. A radical excision of these nodes was performed and arsenical treatment instituted; the surgeon recovered after 5

months. Inoculation of a portion of the biopsied node into a guinea pig caused adenopathy. On repeated passage, there was less evidence of adenopathy and more of septicemia.

Horder (242) cites the case of a surgical colleague who injured his finger while crushing a diseased lymph node in a mortar. Within 3 months, the axillary nodes on the injured side were enlarged and were found at biopsy to be typical of Hodgkin's disease. The patient declined rapidly.

Priesel and Winkelbauer (423) described Hodgkin's disease in a newborn infant whose mother had the acute form of the disease at the time of her pregnancy. They considered this to be an example of intrauterine transmission. von Braitenberg (531) described generalized Hodgkin's disease with marked involvement of the liver in a newborn infant. Though he could not find the disease in the mother, he was of the opinion that it was present, and that the case was another example of placental transmission.

Tyzzer (517) attempted autoinoculation of numerous lymphomatous tissues. He implanted a node of a 17 year old girl, who had had Hodgkin's disease for 4½ years, into a different location subcutaneously. There was no trace of the implant after 4 days. Tyzzer also found that autoinjection of leukemic blood subcutaneously produces slight local tenderness and induration which entirely disappear before the time of the next inoculation several days later. He observed that, in lymphoma, organs may be full of tumor cells yet free of gross lesions; he suggests this indicates that certain tissues are immune to metastases of a certain tumor type. It may well be that the disseminated cells do not have potentialities for giving rise to new foci under the specific conditions existing at a given time and later with changes in immunologic equilibrium may produce widespread tumefaction.

7. MICROBIOLOGIC STUDIES

Because lymph nodes are important stations for defense against micro-organisms, the common bacteria can be cultured from many normal nodes (40). Bloomfield (40) made a study of the bacteria found in normal and diseased lymph nodes and isolated 29 strains of organisms, none of which could be shown to bear an etiologic relationship to diseases of the lymph nodes. Diseased nodes of all types more frequently contain bacteria than do normal nodes possibly because they are less efficient in destroying them (474). It is not unusual, therefore, that Hodgkin's nodes are reported to contain various types of micro-organisms on smear and culture.

Using nodes from 10 cases of Hodgkin's disease, 20 cases of other lymphomatous diseases and 10 miscellaneous cancers involving lymph nodes, Torrey (508) cultured diphtheroids from 4 of the 10 Hodgkin's patients and 18 of the remaining 30 cases. An anaerobic bacillus was consistently cultured from the Hodgkin's nodes and from 12 of the other miscellaneous diseased nodes. No immune response to this bacillus was found in the serum of the Hodgkin's patients investigated. Animal inoculations in monkeys and guinea pigs resulted in a moderate transitory immune response.

It is possible to assume that the irregular appearance of various organisms in the diseased nodes is significant if we accept the notion of Fitchett and Weidman (155) that "peculiarities in the constitution of persons or of their lymph nodes might permit the development of Hodgkin's disease from... infection due to tuberculosis, the diphtheroid bacillus and other organisms which from time to time have been cited as etiologic agents in Hodgkin's disease." Desjardins (128) states that "the factor immediately responsible for lymphoblastomatous hyperplasia of the lymphoid structures is chronic infection of any kind."

The advancing of a theory of multiple causation is in some cases the result of repeated failures to indict a single causative agent. Bacilli and cocci of many varieties, diphtheroids, fungi, yeasts, spirochetes, tubercle bacilli, Brucella and virus agents have been incriminated but there has not been sufficient evidence to establish any of these as the etiologic agent of Hodgkin's disease.

Murray (396) reported that the experiments of Delbet tend to show that the disease is due to a certain bacillus; he obtained a bacillus on pure culture which, when inoculated into a dog, caused lymph node enlargement and emaciation. Abram (2) recovered a gram negative micrococcus from the blood. Abram considers the micrococcus as a secondary infecting agent and noted that "during the period of secondary infection the glandular swellings diminished greatly in size, to again enlarge when the organisms disappeared from the blood." Billings and Rosenow state that cocci predominate in the lymph nodes longest involved while bacilli predominate in the more recently involved lymph nodes (37). Litterer (333) reports that *Staphylococcus albus* is associated with exacerbations. Twort (514) found many organisms in direct smear and culture of tissues from 61 cases but found no organism with any degree of consistancy. Jackson and Parker (262) found a gram positive, anaerobic, gas forming bacillus in many nodes and in the blood of some acutely febrile cases; this

same organism was also found in control nodes. When used as an antigen in agglutination and skin test reactions, the results were negative; the bacilli were nonpathogenic for mice. Repeated blood cultures have failed to indicate the presence of microorganisms (23, 115, 347). Splenic puncture has also yielded negative results in this respect. Others (347) have examined blood films directly with negative results.

Diphtheroids.—During the period between 1911 and 1915, Bunting (51) and Bunting and Yates (52-57) reported the isolation of diphtheroid organisms usually in pure and occasionally in mixed cultures from the nodes of their patients with Hodgkin's disease. The bacteria were pleomorphic, showing coccoid, bacillary and filamentous forms. They repeatedly injected monkeys with living organisms and produced "progressive enlargement of a single group of lymph nodes which show histological changes identical with those seen in humans when the disease is of the same duration, namely: chronic lymphadenitis with atypical proliferation of the endothelial cells, beginning proliferation of the stroma, well-marked eosinophilic infiltration and periglandular fibrosis." In addition, they found that the "blood picture showed the changes of human patients with the disease" and concluded: "We feel assured of the etiologic relationship of the organism, which we have designated corynebacterium hodgkini, to the disease." The authors reasoned that the pathogenesis of Hodgkin's disease in humans involved the discharge of the diphtheroid organisms and their products into the surrounding tissues from a chronic focus of infection, especially in the nose and throat. It was postulated that the organisms were filtered out by the regional lymph nodes and produced Hodgkin's lesions in those structures. In support of this theory, they cited the ease with which diphtheroids could be isolated from the nose, throat, teeth and tonsils of Hodgkin's patients.

A year later, these authors reported: "While the histological picture of the enlarged lymph nodes of the monkey leaves no question as to the relation of the lesion to that of human Hodgkin's disease of the same duration, the great difficulty seems to be to secure infection and at the time time to avoid so great virulence as to produce extensive necrosis, softening, and even suppuration. The working space between these two limits seems very narrow. At present, our results indicate that the survival of an animal for the requisite length of time is all that is needed for the demonstration of the chronic lymph node picture seen in a well-developed case of Hodgkin's disease. Autopsy of monkeys while showing much necrosis and pus, likewise showed tissue like Hodgkin's disease in the wall of lymph node abscesses and in the spleen."

Billings and Rosenow (37), Fox (161) and Ayrosa (16) each found diphtheroid organisms on culture of Hodgkin's nodes. Ayrosa was not able to isolate the organism from control nodes; a complement fixation test which he performed, using the organism as the antigen, "was slightly positive in a case of Hodgkin's disease and negative in other adenopathies." Although he was unable to reproduce the lesions in animals with these organisms, as claimed by Bunting and Yates, he found that the diphtheroid organism exhibited a marked predilection for the lymphatic system and following inoculation produced infarction, slight fibrosis and eosinophilia in these structures. Limper (330) cultured diphtheroids from the blood stream of a child with tuberculosis and Hodgkin's disease. Simonds (474) reported that some authors considered the granules of Fraenkel and Much to be diphtheroid organisms. Smith (480) recovered diphtheroids in pure culture from the nodes of 4 Hodgkin's disease patients. He injected the organisms into guinea pigs, rabbits and monkeys with no effect. Axillary injection in the latter animals caused nonspecific adenopathy which later regressed.

Smith (480) noted that the conditions under which the cultures were prepared by most workers were not always consistent with the maintenance of absolute sterility. Cunningham (115) sharply criticized the studies implicating the diphtherotid organism as an etiologic agent. When he used the routine or usual technic employed by others, the organisms were cultivated from all types of lymph nodes; whereas, when rigid technic was enforced, organisms were found neither in Hodgkin's nor control nodes. Moreover, he did not think the lesions produced in monkeys were comparable to those of human Hodgkin's disease. "Emulsions of many types of tissues will cause lymphatic necrosis" if the injection is repeated. The resulting necrosis may be due to an anaphylactic reaction.

Fox (161) found diphtheroids in nodes of Hodgkin's disease, chronic atrophic arthritis and metastatic cancer. The organisms isolated from Hodgkin's nodes were of no one bacterial variety with definite morphologic and cultural characteristics. Baldridge, Rohner and Hansmann (20) cultivated diphtheroid organisms from 3 of 6 cases of infectious mononucleosis. They found these organisms to be nonpathogenic for guinea pigs and recorded negative serologic tests when the organisms were

used as antigens. Twort (514) after extensive trial, could not confirm the presence of diphtheroid organisms in Hodgkin's disease.

Although Stewart (496) found diphtheroids in nodes of 4 out of 5 cases of Hodgkin's disease, "no agglutinins, precipitins, complement fixing bodies or bacteriotropic substances were demonstrated to these organisms in the serum of patients with Hodgkin's disease or in normal controls." Animal inoculations were performed: cotton plugs or bone saturated with heavy suspensions of living organisms were introduced intraperitoneally and suspensions of organisms were inoculated intravenously, subcutaneously and intraperitoneally into 5 monkeys. Although 2 of the animals exhibited slight swelling of regional nodes following implantation of the cotton plugs at autopsy 2½ and 11 months after inoculation respectively, no abnormalities were found. No lesions were found in dogs, inoculated in a similar manner, at autopsy 6 months after inoculation. Two chickens were inoculated with bone which had been incubated with the organism; although the chickens died after having exhibited anorexia, anemia and weakness, there were no lesions at autopsy. Two rabbits were inoculated with crushed lymph nodes and diphtheroid organisms; they died in less than 1 month with weight loss, anorexia and paralysis of the hind quarters; no lesions typical of Hodgkin's disease were found at autopsy. The author concludes that "there is no evidence that corynebacteria are etiologic in Hodgkin's disease."

A vaccine, prepared from the diphtheroids, was used by several groups without success (37, 113, 164, 377).

Present day references to the diphtheroids as etiologic agents are made only in historical review; it is generally agreed that there is no evidence for the etiologic relationship between the diphtheroid organism and Hodgkin's disease.

Animal and vegetable parasites.—Many of the manifestations of Hodgkin's disease such as eosinophilia, relapsing fever, adenopathy and fatal termination may be explained on the basis of a fungal, yeast or protozoan etiologic agent since organisms of this variety cause granulomatous lesions. It is, therefore, not surprising that occasional descriptions of the association between animal and vegetable parasitic diseases and Hodgkin's disease have excited interest.

Torulosis is a disease of world-wide distribution and has been described in association with Hodgkin's disease several times (87, 155, 406). Characteristically it affects active adults, males twice as often as females. The majority of patients die within 6 months but survival beyond this point usually permits a life expectancy of 2 to 4 years. The clinical picture usually includes a chronic meningitis, and the characteristic lesion is a miliary granulomatous nodule resembling the tubercle. The portal of entry of the yeast is thought to be the lung (532). There is one report of the isolation of the torula organisms from Hodgkin's lesions (406) and in another patient successive steps have been traced between the "obviously torular process in the spleen and the processes definitely due to Hodgkin's disease in the lymph nodes" (155). Failure to isolate the yeast consistently from Hodgkin's lesions does not preclude its etiologic role; "the possibility must be kept in mind that there are ultramicroscopic forms of torula" (155). Cohen (87) maintains that of 78 cases of torulosis reported in the literature, at least 10% were associated with Hodgkin's disease. This he says "is too frequent an occurrence to be a mere coincidence, but so far the relationship of the two diseases has not been established."

Miscellaneous reports concerning other organisms of this group are the following:

Visceral moniliasis and Hodgkin's disease were found in the same patient with isolated Sternberg-Reed cells grouped about some of the monilial lesions (229). Kofoid, Boyers and Swezey (298) described a case of Hodgkin's disease complicated by amoebiasis. They maintained that many so-called Sternberg-Reed cells were in reality amoebae and that the latter could be differentiated from tissue cells by the difference in chromosome pattern and number that is apparent during mitosis. Twort (514) and Schreiner and Mattick (457) could not verify Kofoid and associates' findings.

The following case is reported from Ankara (572). A 38 year old male complained of fever and prostration accompanied by splenomegaly, hepatomegaly and lymphadenopathy. "Biopsy of an enlarged lymph node showed an inflammatory infiltration rich in eosinophils with numerous Sternberg cells. Because of these findings, a diagnosis of lymphogranulomatosis was made" Aspiration biopsy of the spleen and liver at a later date revealed *Histoplasma capsulata;* this was confirmed at autopsy at which time the organisms were found in the same organs.

A group of investigators studying the changes in the Sternberg-Reed cell concluded that the formation of filaments and rosettes in the cytoplasm at the same time that the nucleus was destroyed was suggestive that the cell was the burying ground of

a pathogen intermediate in type between the Actinomyces and the acid fast bacilli (312).

These varied etiologic suggestions were put to rigid experimental test by the workers of the Rose Research group (112, 188, 499). Systematic search for evidence of mycotic infection was made by means of smear and culture. Yeasts were grown from the nodes of 17 of 23 cases of Hodgkin's disease and from 20 of 36 control cases. These yeasts caused granulomatous lesions in animals but no antibodies were found in the serum of patients from whom the yeasts were isolated. Similarly, sporothrix, aspergillus and coccidioides when tested produced granuloma in experimental animals. While these lesions bore a general resemblance to those of Hodgkin's disease, the differences were significant. The isolation of these organisms from control nodes and their failure to produce positive immunologic results were considered sufficient evidence to prove that the presence of fungus was devoid of etiologic significance. They conclude: "No evidence was found that lymphadenoma is due to a mycotic infection."

Spirochetes.—Simonds (474) believes that syphilitic cases with histologic resemblance to Hodgkin's disease occur too rarely to be significant. Proescher and White (quoted from Simonds [474]), in 1907, reported finding spirochetes in the lymph nodes of a case of Hodgkin's disease. MacCallum, Longcope, Karsner and others were unable to confirm the findings of Proescher and White. Gordon (204, 205) examined 6 cases thoroughly and found no spirochetes. On silver impregnation of sections, small curved filaments with pointed ends were seen by Gordon. Since they were also found in control nodes in equal numbers, this finding was not considered significant. The author considered these non-specific findings as a possible explanation of the results of Proescher and White.

Brucella organisms.—Parsons and Poston (410) called attention to the coexistance of Hodgkin's disease and Brucella infection in 1939. Their first case "was definitely one of Brucellosis." When first seen, the opsonocytophagic index was elevated and nodes were suggestive of non-specific adenitis. Before the patient died, lesions indistinguishable from Hodgkin's disease were found.

Parsons, Poston and Wise (411) state that chronic brucellosis of the glandular type prevalent in the area (North Carolina) in which their work was done cannot be differentiated from Hodgkin's disease by either histologic or clinical methods.

Wise and Poston (558) report the isolation of Brucella organisms from a total of 14 consecutive cases of Hodgkin's disease. Organisms were isolated either from the blood, affected lymph nodes, or both. Sixty-seven control nodes were examined and Brucella isolated only once; repeated blood cultures from these patients were negative with 1 exception. Furthermore, "cultures yielding Brucella have been obtained with greater frequency when Hodgkin's disease was actively progressing than when it was subacute or temporarily arrested" (421, 558). Forbus and Gunter (158), working in the same laboratory, found the coexistance of Brucella infection and Hodgkin's disease in 4 more cases. Bernreiter (33) described a case of Hodgkin's disease in which Brucella agglutinins were present in high titer and the brucellin skin test was positive. Treatment with sulfanilimide and blood transfusion resulted in weight gain, return of appetite and fall in the sedimentation rate from 20 to 10 mm. per hour. Burger and Lehman (58) cultured the blood of 3 cases of Hodgkin's disease; Brucella was isolated in one case. Gall and Page (182) report an interesting case which could not be diagnosed before death or at autopsy. Neither Hodgkin's disease nor Brucellosis could be ruled out.

Bloomfield (41) states that the clinical picture of Hodgkin's disease and brucellosis are not always easy to differentiate since they both occasionally exhibit the following clinical features: adenopathy, prolonged undulating fever, splenomegaly and eosinophilia. In 50 unselected case reports of brucellosis, in which the state of the lymph nodes is specifically mentioned, enlargement occurred in 29 cases or 58%. In 26% enlargement was confined to the cervical nodes and in the remaining 32% other nodes were enlarged or there was general superficial lymphadenopathy. The condition of the lymph nodes at autopsy was not well described. Some of the descriptive terms used were "granulomatous," "tubercle-like" and "Hodgkin-like." Bloomfield concludes that because of the possibility of confusing Brucella infection and Hodgkin's disease, it is important to have accurate information about enlargement of superficial lymph nodes in the former. In some of these cases, lymphadenitis is a specific manifestation of brucellosis, and if undulating fever and splenomegaly are also present, the condition can be easily confused with Hodgkin's disease.

Agglutinin-adsorption tests and the bacteriostatic reactions of dyes were used by Wise and Poston to ascertain the species of Brucella; the opsonocytophagic indices of the patient's blood were also determined. "A sufficient correlation has been found between the cultural and immunological manifestations and the course of these patients to justify the

belief that the Brucella infection directly influences the syndrome of Hodgkin's disease. The frequent lack of evidence of an immune response when Brucella could be isolated from blood cultures during recurrences of Hodgkin's disease has been very striking. Maximum clinical improvement has been correlated with the presence of serum agglutinins and significant degrees of phagocytosis for Brucella. . ."

Forbus and Gunter (158) inoculated 54 guinea pigs intraperitoneally with tissue suspensions from four Hodgkin's patients; these tissues were said to contain Brucella organisms on culture. No lesion typical of brucellosis or Hodgkin's disease was produced. Although small areas suggestive of reticuloendothelial stimulation were found in 7 guinea pigs, these areas did not yield Brucella organisms on culture. The Brucella organisms isolated from 5 Hodgkin's patients were inoculated into a total of 169 guinea pigs. Four of the 5 strains produced "a mild form of guinea pig Brucellosis," in 51 of the 153 inoculated animals. The fifth strain was not pathogenic for the 16 guinea pigs inoculated. One of the strains required "huge doses of organisms" for the elicitation of positive results. The histopathologic appearance of the lesions is similar to that of typical guinea pig brucellosis. Two variants of special significance are described as follows: in the enlarged lymph nodes which occurred following inoculation, there was a complete and uniform replacement of the lymphoid tissue by "reticuloendothelial reaction" which appeared to take place through the coalescence of many foci of proliferation. The second variant was the rapid epithelioid transformation of the macrophages resulting in a characteristic granulomatous lesion with multiple necrotic areas which were said to be similar to the lesions of Hodgkin's disease. These lesions all appeared to be progressing and no "healing changes" except fibrosis were noted. The lesions were of 5 months' duration when examined and for this reason the authors concluded that brucellosis of the guinea pig may be a highly chronic disease, the end stages of which have not been satisfactorily studied. Using bacterial stains the authors were unable to demonstrate Brucella in the tissues of inoculated guinea pigs or of Hodgkin's patients from which Brucella had been isolated. While the organisms isolated from patients with Hodgkin's disease were capable of producing typical experimental brucellosis in the guinea pig, they appeared to be less virulent than similar organisms isolated from natural infections in the lower animals.

Prolonged inoculation of swine with Br. suis cultured from Hodgkin's nodes resulted in adenopathy. Although the microscopic appearance was said to be similar to that seen in human Hodgkin's disease, no comparable clinical disease was produced (47).

Treatment by Wise and Poston (558) was designed to combat the existing Brucella infection in order to study the influence of this infection on the course of Hodgkin's disease. A definite and often striking decrease in the size of the enlarged lymph nodes was observed after administration of sulfanilimide and sulfapyridine. Immune serums were also used but proved ineffective. Since further investigation revealed that the Brucella organisms isolated from many of the Hodgkin's patients had capsules and were antigenically different from the laboratory strains, it was concluded that further consideration should be given to the immunologic specificity of these sera.

Many individual workers in other sections of the country have been unsuccessful in cultivating Brucella from patients with Hodgkin's disease. In a personal communication to Meyer (380), E. A. Birge reports that he cultured specimens from lymph nodes of 10 patients with Hodgkin's disease but could find no Brucella organisms. Hoster, Doan and Schumacher (247) studied a series of 71 patients in an attempt to elucidate this question. Thirty-five had proven Hodgkin's disease, while 36 had miscellaneous disorders of the reticulo-endothelial system; all were natives of Ohio or the Northern Central United States. The method of Poston (421) for the isolation of Brucella was used; nose and throat secretions, urine, blood, spleen, liver, lymph nodes and bone marrows were cultured. No organisms of the Brucella group were found. The brucellergen skin test was positive after 48 hours in 3 patients with Hodgkin's disease. Significant agglutinin titers for Brucella were not found. The opsonocytophagic indices were not elevated. Moreover, the distribution of brucellosis (Bang's disease) in cattle throughout the United States reveals no parallel to the recorded mortality of Hodgkin's disease or brucellosis in man.

The opinion (244) concerning the present status of Brucella in the etiology of Hodgkin's disease held by the majority of the investigators mentioned above is best summarized by the statement of Chester Jones (276), "I should like to comment on the question of Brucellosis. I saw a good many of Forbus's cases. . .I think that they (Forbus and associates) are in general agreement now that Brucellosis has nothing to do with Hodgkin's disease. In the neighborhood of Durham Brucellosis is endemic and a good many people in the community have it. Its presence in Hodgkin's disease was simply an incidental finding."

Tubercle bacilli.—The volume of clinical material which links tuberculosis and Hodgkin's disease is very large. Their clinico-pathologic points of similarity and frequent association in the same patient have led numerous investigators to accept the tuberculous etiology of Hodgkin's disease (31, 170, 328, 346, 408, 493, 520, 525). Sternberg was the first to point out a possible relation between the two diseases. The failure of Sternberg and others to produce unequivocal evidence and the former's subsequent retrenchment from his original position caused a subsidence of general support of this view. The question was again raised by the experiments of Fraenkel and Much (170). These authors found gram-positive, granular rods in Hodgkin's lymph nodes and believed them to be a form of tubercle bacilli. When investigation failed to confirm their findings and failed to support their interpretations, interest in the tuberculous etiology again decreased. It was again revived by the report of L'Esperance (322); in a small number of cases observed by her, avian tubercle bacilli were found to be associated with the disease. The findings of this author were not confirmed by later investigators.

A few points of view concerning the tuberculous etiology of Hodgkin's disease are cited (538):

1. Hodgkin's disease is of tuberculous origin and represents an atypical reaction of the host to the organism of tuberculosis (492).

2. Hodgkin's disease is an expression of atypical tuberculosis produced by toxins from inert or non-extending foci. The tuberculosis sometimes seen late in the disease may be a flare-up of these foci or a return to type of the atypical lesions (538).

3. Hodgkin's disease is a tumor in which tubercle bacilli play the part of the excitant (538).

4. Hodgkin's disease may be produced by the "filterable elements of the tuberculous virus" (538).

5. Tuberculosis finds in patients with Hodgkin's disease a soil that is favorable for its development (563); old, healed forms become active when the reticuloendothelial system, "so important in the defense against tuberculosis" is blocked by Hodgkin's disease (474).

6. There is a facultative symbiosis between tubercle bacilli and the agent of Hodgkin's disease (474).

7. The hyperplastic form of lymph node tuberculosis may be almost indistinguishable from Hodgkin's disease microscopically (287, 439).

8. Tuberculosis is a secondary invader in Hodgkin's disease and is not of etiologic significance (334).

Arguments frequently advanced in favor of the relationship between Hodgkin's disease and tuberculosis include:

1. The frequent (15%) family history of tuberculosis associated with Hodgkin's disease (92). Ziegler (571) found this association in 9 of 54 cases. In Uddstromer's study (518) a familial history of tuberculosis was found in 25.5% of 479 cases. In 706 cases of normal individuals chosen at random, however, a family history of tuberculosis was obtained in 29%.

2. The occasional history of contact with tuberculosis before the onset of Hodgkin's disease (96).

3. The "similar" histopathologic appearance of both lesions in selected cases (439).

4. The frequent finding of acid fast bacilli in Hodgkin's lesions (81, 322, 431, 474, 493).

5. Animals inoculated with tissues of Hodgkin's disease occasionally develop tuberculosis (81, 322, 474, 493, 524).

6. Occasionally the tuberculosis which results from injection of Hodgkin's tissue into guinea pigs is indistinguishable from Hodgkins' disease (459, 524).

7. The blood count of patients with Hodgkin's disease is similar to that observed in tuberculosis (50, 559).

8. The clinical course (low grade fever, weight loss, weakness, anemia and cachexia) is like that of tuberculosis (431, 474).

9. The fact that Hodgkin's disease pursues an inevitably fatal course is not a valid argument against its tuberculous nature.

10. The occasional transformation of Boeck's sarcoid, considered by some to be a tuberculous process, to Hodgkin's disease and the simultaneous finding of the two diseases in the same patient has been noted (96).

There are numerous answers to each of these arguments:

1 and 2. With the decline in the total number of cases of tuberculosis in the general population, a positive family history and history of contact are less frequently obtained.

3. The histologic differences between diffuse tuberculosis of the lymph nodes and Hodgkin's disease were pointed out by Karsner (286). The tuberculous lesions which resemble Hodgkin's disease are due to accumulation of megakaryocytes in the foci of the former (375).

4. The fact that acid fast organisms are found in Hodgkin's disease is not remarkable. Lymph nodes are filtering stations for bacteria and the tubercle bacillus is not infrequently found in so-called normal nodes (81). Moreover, tubercles in Hodgkin's nodes are easily distinguishable from

the remainder of the Hodgkin's tissue present (431).

5 and 6. Animals inoculated with all types of lymph node suspensions may develop tuberculosis since acid fast bacilli may be accidental invaders of lymph nodes (81).

7 and 8. The resemblance of the blood and clinical findings does not establish the identical nature of two diseases (81).

9. There is no doubt that many untreated cases of tuberculosis recover; and there is great doubt that any patient with Hodgkin's disease recovers.

10. There is no proven relationship between Boeck's sarcoid and tuberculosis.

One of the most frequent arguments used to support the causal relationship of the two diseases is the frequent finding of tuberculous lesions in Hodgkin's disease patients at postmortem. Wallhauser (538) reviewed 151 autopsy reports obtained from the literature and concluded that Hodgkin's disease is associated with tuberculosis in 20% of cases. Parker, Jackson, Bethea and Otis (408) reviewed 78 cases of Hodgkin's disease in which tuberculosis was associated with it in 38.5%. An analysis of their own data reveals an association in 10 of 30 cases investigated. Jackson and Parker (262) later reported that Hodgkin's disease is coexistent with tuberculosis in 20% of cases.

Although Lubarsch (340) considered the association to be more frequent than can be accounted for by chance, Lemon (320), Uddstromer (518) and Burger and Lehman (58) report the incidence of tuberculosis in living Hodgkin's patients to be no more frequent than that of the general population. In 6 of 213 cases of granuloma "proved tuberculosis adenitis had preceded by months or years the development of Hodgkin's granuloma in the same region" (266). Of 400 consecutive general autopsies (408), a total of 19% showed tuberculosis. Fourteen per cent of patients with cancer had tuberculosis and 17% of patients with other lymphomas had tuberculosis. Although active tuberculosis was found in 20% of Parker and associates' 30 Hodgkin's disease patients at post mortem, it was found in only 11% of general autopsies, in 5.7% of cases with cancer and in 6% of cases with lymphoma other than Hodgkin's. The percentage of healed tuberculosis did not differ materially in the various types of lymphoma except that no cases of lymphatic leukemia exhibited either healed or active tuberculosis. The low incidence of tuberculosis in lymphomas other than Hodgkin's disease is not explained. Parker, Jackson, Bethea and Otis suggest the possibility that the large number of lymphocytes in general characteristic of certain lymphoma might protect against disease produced by the tubercle bacillus. In the case of Hodgkin's disease, they considered the higher incidence of tuberculosis to be significant and thought that one disease either predisposes to the other or that the same constitutional type is susceptible to both.

Death due to the tuberculous process in patients with Hodgkin's disease has been reported rather frequently (81, 322, 431, 471, 474, 538). The role of roentgen radiation in reactivating latent foci of tuberculosis has not been accurately determined but may have a bearing on the frequency with which rapidly advancing tuberculosis is responsible for the death of many patients with Hodgkin's disease. Recent figures suggest that the association between Hodgkin's disease and tuberculosis is becoming less frequent (119). The incidence of Hodgkin's disease among hospitalized tuberculous patients is about 0.3% (based on 2,297 admissions of tuberculous patients at the Boston City Hospital), a figure which is not significantly different from the occurrence of Hodgkin's disease in general hospital admissions (262). Moreover, the reported distribution of mortality due to human tuberculosis in the United States is entirely dissimilar to that of Hodgkin's disease (244).

Tuberculin test.—The interesting behavior of the tuberculin test in Hodgkin's disease (see p. 17) is another argument in favor of an interdependency or relationship between the two conditions. The tuberculin anergy which is said to be characteristic of the Hodgkin's patient has led to the conclusion that "either the process of Hodgkin's disease desensitizes its victims to these tuberculo-proteins or Hodgkin's disease usually occurs in persons in whom the development of normal sensitization to the tuberculin protein is impossible. It is difficult to conceive of either of these phenomena as occurring in a disease absolutely unrelated to tuberculosis" (487). The fact that the tuberculin test sometimes becomes strongly positive after effective roentgen therapy (262) suggests that roentgen therapy either restores sensitization by improving the general health of the patient or produces sensitization by activating latent foci.

Additional evidence concerning the association of Hodgkin's disease and tuberculosis.—Numerous forms and varieties of tubercle bacilli have been implicated in the etiology of Hodgkin's disease. Martinolli (361) suggests that Hodgkin's disease is caused by a filter-passing form of the tubercle bacillus. He believes that the existence of such a form since inoculation of guinea pigs with material

from fetal livers and spleens obtained from tuberculous mothers caused tuberculosis in those animals. In one guinea pig "typical Hodgkin's disease was seen."

Altered, degenerate, atypical varieties and forms of low virulence have been suggested as etiologic agents (81, 538). The granules of Much, said to have been found consistently by Fraenkel and Much in Hodgkin's lesions, were considered by Lichtenstein (328) to be defatted tubercle bacilli. Busni (61) and Faure-Beaulieu and Brun (151) report that all atypical forms of the tubercle bacillus, all of the pleomorphic bacteria and cocci and all the diphtheroid organisms which have been isolated from Hodgkin's disease are merely stages in a very complicated life cycle of the tubercle bacillus. One of these stages is said to involve a filter-passing form.

Jackson and Parker (262) reported that, although no growth of tubercle bacilli occurred following culture of nodes, smears made from the apparently sterile surface of the medium occasionally contained acid-fast organisms of an obscure nature.

L'Esperance (321, 322) implicated the avian tubercle bacillus in Hodgkin's disease and suggested that failure to demonstrate the organism was due to the use of laboratory animals which were not susceptible to this organism. "Guinea pigs have a natural resistance to avian infection with a long period of incubation (6 to 18 months) before generalization of the disease. . .Preliminary inoculation with human tubercle baccilli rendered them less resistant to avian infection." However, when established, the lesions are said to have a predilection for the lymph nodes and on section to reveal Sternberg-Reed-like cells. In a series of experiments involving chickens inoculated with lymph nodes from 6 cases of Hodgkin's disease, avian tubercle bacilli were recovered in mixed or pure culture from involved chicken tissues. The results of the tuberculin testing of 12 clinically suspected cases of Hodgkin's disease were presented as additional evidence. L'Esperance concluded that "accumulated evidence presents substantial proof of the etiologic significance of the avian tubercle bacillus in certain clinical forms of Hodgkin's disease."

Stewart and Doan (495) reported that "a high precipitation titre was found in the blood for avian tuberculo-phosphatid" in 26 of 32 cases of Hodgkin's disease. "The non-tuberculous process may alter the physicochemical relation in the blood serum so that precipitation of the colloidal suspension of tuberculo-phosphatid might occur. On the other hand, control cases with lymphosarcoma, leukemia and pseudoleukemia on the whole show lower titres."

Twort (514) studied material from 61 Hodgkin's patients in various stages of the disease. Microscopic sections were examined, tissue and blood cultures were made and animal inoculations were carried out. Twort found Much's granules in occasional sections. The simultaneous inoculation of tubercle bacilli and Hodgkin's nodes resulted in typical tuberculosis. Bacterial cultivation of tubercle bacilli in the presence of Hodgkin's tissue did not produce variants which differed noticeably from those cultivated in the presence of control nodes. Animal inoculation using Hodgkin's nodes as inoculum or in combination with lactic acid (as suggested by Much) did not result in tuberculosis; animals so treated did not become sensitive to tuberculin.

Steiner (486) could not culture tubercle bacilli from material obtained from 15 patients with Hodgkin's disease who had received little or no radiation. Inoculation of the material into 24 guinea pigs caused tuberculosis in only one animal in spite of the fact that thick suspensions prepared from large amounts of the diseased tissues were injected. During the examination of smears from diseased tissues stained by the Ziehl-Neelson method, acid fast granules and debris, suggestive of degenerated bodies of tubercle bacilli, were often seen. In sections of these tissues stained by the Cooper method, the acid fast material appeared to be either granules from eosinophilic leukocytes or debris resulting from the destruction of red blood cells. In addition, Steiner inoculated rabbits, dogs and mice with lymph node extracts from 23 patients, 15 of which had Hodgkin's disease. He allowed the animals to survive for periods ranging from 9 to 18 months but did not observe tuberculous infection in any of the animals.

A search for tubercle bacilli was made by the Rose group (205). Fresh node suspensions from 40 Hodgkin's patients and control preparations from 35 others with diverse lymphoid diseases were injected into guinea pigs. Material from 2 of the Hodgkin's patients and 2 of the control series gave rise to guinea pig tuberculosis. Injection of the lymph node suspensions into mice did not initiate the development of tuberculosis. The authors concluded that the "incidence of tubercle lymphadenoma glands is much the same for controls showing other definite histologic evidence of tubercle."

Denial of the hypothesis that Hodgkin's disease is due to avian infection has come from many sources (205, 249, 262, 311, 375, 487, 496, 520, 538). Medlar and Sasano inoculated rabbits in-

travenously with virulent avian tubercle bacilli. Autopsy study revealed lesions similar to but nevertheless distinguishable from those of Hodgkin's disease. These same lesions could be produced by virulent bovine and human tubercle bacilli. Animals previously inoculated with human tubercle bacilli did not develop either the acute form of tuberculosis or Hodgkin's-like lesions when virulent avian organisms were injected. van Rooyen (520) offers the pertinent reminder that "there are proven cases of avian tuberculosis in man and they are not different from other tuberculosis." The same author inoculated 4 chickens and 4 pigeons with dense emulsions of Hodgkin's lymph nodes and introduced grafts into the liver, peritoneum, and femur shaft and muscle of 5 chickens. None of the animals developed avian tuberculosis. Wallhauser (538) inoculated 6 chickens, Stewart (496) 4 chickens, McGrath (368) 4 chickens and Garrod (188) 3 pigeons by various routes with negative results. The nodes of 15 patients most of whom had not been treated with roentgen radiation were inoculated into 35 chickens, 24 guinea pigs, 18 rabbits, 7 dogs and 3 mice by Steiner (486). Although thick suspensions were used as inoculum and there was over-crowding of animals and prolongation of the experiment for more than 1 year, only 1 chicken and 1 guinea pig developed tuberculosis. Branch (44), reviewing the characteristics of avian tubercle bacilli, stated the precautions recommended by Van Es for preventing spontaneous tuberculosis in fowls and noted the reported rarity of avian tuberculosis in man. He doubted that proof of the etiologic relation between avian tuberculosis and Hodgkin's disease was established.

The most recent work concerning the relation of the tubercle bacillus and Hodgkin's disease is reported by Hoster, Doan and Schumacher (249). Thirty lymph nodes and 3 spleens were obtained from 33 patients with histologically proved Hodgkin's disease during the early stages of the disease. Direct smears were made from diseased tissue and 6 selected media for the isolation of acid-fast organisms were inoculated. All media inoculated were tested for organisms at intervals over a period of 3 months, whether visible colonies were present or not. In addition, 68 guinea pigs, 30 leghorn chickens and 4 rabbits were given subcutaneous and intravenous inoculations of thick emulsions of Hodgkin's tissue. Controls in each animal group were given inoculations of tissues obtained from patients with other diseases. All animals were skin-tested with old tuberculin and human PPD before inoculation and at intervals during the experimental period. Twenty additional guinea pigs were sensitized with killed human tubercle bacilli 8 to 10 days before inoculation with Hodgkin's tissue emulsion. Ten other guinea pigs receiving killed human tubercle bacilli only served as controls. All the animals were autopsied at death or 8 months following inoculation. Fixed tissue sections were made from animal organs and all suspicious lesions were cultured. In all these experiments, no acid-fast organisms were isolated, all skin tests were negative and no tuberculosis was observed in any animal except in those injected with material from 4 control cases with histologically proved tuberculosis. In general agreement with many others, Hoster and associates conclude, "From the results obtained in the present course of study, it is not possible to say that the avian, bovine or human tubercle bacillus sought under the conditions specified, has an etiologic role in Hodgkin's disease." The authors suggest that the negative results obtained indicate that the tubercle bacillus is not usually found in Hodgkin's tissue during the early stages.

The Gordon phenomenon.—The earliest systematic investigation of the virus etiology of Hodgkin's disease was carried on by Gordon and his associates (205). Under his supervision, lymph node emulsions were injected by different routes into the common varieties of laboratory animals. Intraperitoneal and subcutaneous injection in the rhesus monkey gave negative results (205, 480). Intracerebral inoculation in mice was without effect. Fresh suspensions of Hodgkin's nodes injected subcutaneously into the guinea pig resulted in local inflammatory reaction which reaches its maximum size after 5 to 8 days and then regresses. The nodule contained nonspecific inflammatory changes with scattered fibrosis and eosinophilia; these changes were noted following a few control injections as well.

The production of encephalitis in rabbits, a technic which later became known as the Gordon test, is discussed below in detail. All tissues and suspensions were first tested for the presence of organisms by smear and culture with negative results. Nodes were removed from patients with Hodgkin's disease, ground and allowed to extract in broth in a refrigerator after which they were inoculated intracerebrally into rabbits. Two to 6 days after inoculation, a characteristic syndrome was produced consisting of muscular rigidity, spasm, paralysis, progressive wasting and death. Attempts to isolate bacteria from the brain or blood stream of the inoculated animal were unsuccessful. Gordon found that in animals that died following injection the cerebellum contained evidence of an almost complete loss of Purkinje cells and a marked glial

reaction in the region of the Purkinje layer. In addition, in fatal cases there was patchy perivascular lymphocytic infiltration and a mild meningeal reaction. It was found that 60 to 75% of nodes from patients with Hodgkin's disease produced this syndrome in rabbits following intracerebral inoculation. Nodes from control cases of lymphatic leukemia, lymphosarcoma, melanotic sarcoma, "periosteal sarcoma," carcinoma, "endothelial tubercle" and chronic adenitis gave negative results in all but 2% of the cases. The rabbits which recovered presented no evidence of histologic abnormalities.

Gordon subsequently altered the preparation of the suspension of macerated nodes in an attempt to elucidate the nature of the encephalitogenic agent. Dessication followed by resuspension appeared to enhance the potency of the material and storage of the dessicated nodes for 2 years in one case was followed by a positive test. The agent resisted freezing and heating at 65° C. for 30 minutes, whereas at 70° C. for 30 minutes it was partially inactivated, and at 100° C. for 30 minutes it was completely inactivated. Suspension in broth resulted in a more potent material than suspension in distilled water. The encephalitogenic agent was present in the supernatant fluid following centrifugation at 3,200 r.p.m.; it was not present in the filtrate following passage through a Chamberland filter. Inoculation with human serum enhanced the potency of the suspensions while addition of rabbit brain interfered with the test. Attempts to transmit the encephalitis from an affected to a normal rabbit met with failure. Although initially Gordon reported that animals who recovered had some immunity to further inoculation, this was not confirmed by later investigation (143, 254, 489, 523).

Using a staining technic which was said to demonstrate virus elementary bodies, Gordon found that broth suspensions of Hodgkin's nodes contained "large numbers of minute granules of the same order as the elementary bodies of vaccinia and psittacosis." Gordon's preparation of a vaccine containing these bodies has been described under the section dealing with treatment.

At a later date it was found that the Gordon phenomenon could be produced in guinea pigs following intracerebral inoculation. At autopsy it was noted that there was congestion and enlargement of the lymph nodes in the axilla and groin.

Gordon's findings in general were confirmed (143, 217, 254, 489, 523). Doubt concerning his hypothesis that the responsible agent was virus in nature arose when it was noted that encephalitogenic activity, similar in every observable aspect to that present in Hodgkin's nodes, was exhibited in some cases by the normal bone marrow, spleen, leukocytes and pus of human beings but not of dogs and rabbits (143, 176, 177, 290, 344, 511).

Friedemann (177) considered that the agent was similar to the proteolytic ferment of Jockmann which is derived from bone marrow and spleen. Both the Gordon agent and Jockmann's ferment resist heat similarly and are insoluble in acetone and methyl alcohol. Jockmann's method for the isolation of the ferment may be summarized as follows:

Incubate tissue for 24 to 48 hours at 55° C. Add 5 volumes of alcohol-ether (2 volumes of absolute alcohol to 1 of ether). After 24 hours at room temperature remove and discard the supernatant fluid. Dry the resulting deposit in a dessicator and mix with an equal volume of 50% glycerine in water. After 24 hours at room temperature, discard the deposit and mix the supernatant fluid with 5 times its volume of alcohol-ether. Allow to stand for 24 hours to allow time for precipitation. The precipitate contains the Jockman ferment.

Since a positive Gordon test was obtained following extraction according to the Jockmann method, Friedemann concluded that the agent and the ferment were one and the same and that the agent could not be a virus since no living organism could withstand the manipulation involved in the preparation of the ferment. MacKenzie and van Rooyen (344) failed to correlate Jockmann ferment with encephalitogenic activity. Although MacKenzie and van Rooyen stated that the Jockmann extracts often resulted in a positive test, extraction of a node which did not possess encephalitis-producing properties nevertheless yielded a type of ferment which in turn failed to result in a positive test. Moreover, after experimenting with bacteria, MacKenzie and van Rooyen demonstrated that the Jockmann extraction did not destroy all forms of living organisms, especially those which form spores.

Nevertheless, numerous factors were found to be inconsistent with the virus nature of the agent responsible for the Gordon phenomenon: (144, 292, 489, 511, 523).

1. Unsuccessful serial transmission (290, 292).
2. Absence of immunity following recovery (143).
3. Absence of complement fixing antibodies and precipitins in rabbit serum (143).
4. Absence of neutralizing factors in the patient's serum against the agent (143).
5. Failure of "super-centrifugation" to sediment the agent (143).
6. Retention of activity following the Jockmann ferment procedure.

7. Distribution in a wide variety of normal tissues.
8. Lack of evidence of successful cultivation in vitro (562).
9. Absence of inclusion bodies in the nerve cells of affected rabbits (521).

Turner, Jackson and Parker (511) examined diseased lymph nodes, control nodes and normal tissues and found that they could correlate encephalitogenic activity with the presence of eosinophils in human lesions and normal bone marrow. They made tests with leukocytic creams and discovered that suspensions containing more than 2,000 eosinophils per cu. mm. produced a paralysis "indistinguishable from that seen in the positive Gordon test, while the numbers of any other type of white cell appeared to exert no such influence." Moreover, they found that they could predict which lymph nodes would give a positive Gordon test. Initial counts of 10 to 20 eosinophils per oil immersion field and 2 weeks' extraction of the material were necessary for the appearance of a positive test when the material was inoculated. Initial counts of 1.5 to 3 eosinophils were sufficient to produce a positive test after the material had been extracted for several months. The authors believe that the agent may be "similar to or possibly identical with the Charcot-Leyden crystal which has long been looked upon as a derivative of the primate eosinophil." Edwards (144) also found evidence suggesting an association between eosinophilia and the appearance of the Gordon phenomenon. McNaught (371) in 1938 from a study of the literature and 13 of his own cases concluded that "the Gordon test is of no more practical value in the diagnosis of Hodgkin's disease than is the finding of eosinophils in the lymph nodes."

Although Steiner (489) failed to find a correlation between the presence of eosinophils and the Gordon test in a few cases, it is generally accepted that the presence of these cells is necessary for a positive test. van Rooyen (521) stated that the rabbit brain, damaged in the occipital area by injections of turpentine, aleuronat, sodium nucleinate, quinine-urethane, powdered glass and dead bacteria does not give rise to a Gordon syndrome. Friedemann (177) noted that the syndrome differed from the known effects of chemical substances in that it was progressive.

Viruses.—Virus agents can produce granulomatous lesions which in some instances may resemble true neoplasms (242, 448, 510). One group of investigators, including Rous (448), has presented evidence in favor of the virus etiology of neoplasms as a group. This school of thought considers the tumor virus to be "an actuating carcinogen" differing from provocative carcinogens such as methylcholanthrene, tar, roentgen rays and some estrogens. The actuating carcinogen, a virus, is transmitted to the offspring during intrauterine life or through the milk of the mother and lies dormant in the body until "provocative carcinogens" change the cell milieu to a favorable one and thus permits the actuating carcinogen to incite tumor growth. The virus thus stirred into activity is a variant which is not transmissible and hence a "dead-end agent"; only the original reservoir of virus is tumor forming, and it is from this reservoir that the progeny receives its actuating carcinogen.

Without in any way giving their approval to the theory of virus etiology of true neoplasms, many investigators have postulated that a virus agent may be responsible for Hodgkin's disease (118, 205, 212, 245, 370, 514, 547). Their conclusions are reached purely by inference based on clinicopathologic manifestations of the disease and its similarity to virus tumors in animals. The observation of Desjardins (128) and others (246, 370) are consistent with this hypothesis; Bersack's interesting patient (36) who exhibited "terminal blood stream spread...without any evidence of embolic cellular element dissemination, is consistent with a virus etiology of Hodgkin's disease."

Tissue culture studies.—Additional experimental evidence concerning this thesis has not appeared in the recent literature with the exception of the preliminary reports of Grand (212) and Hoster (245).

Grand's experimental material is quoted below in full (212).

"In the literature, the etiology of Hodgkin's disease has been ascribed to numerous agencies. Among these, bacterial and virus infections have been included.

This report is based on nodes from 35 cases of Hodgkin's disease, obtained surgically from Memorial Hospital, New York. The lymph nodes were from early and late stages of the disease. As controls, normal lymph nodes from 12 radical mastectomy cases were used, also nodes from various lymphomas (20 lymphosarcomas, 15 leukemias) and from 23 metastatic carcinomas and 10 lymphadenitis cases.

The nodes were cut into small fragments (explants, about 1 cu. mm. in size) from which tissue cultures were prepared in the usual way. The medium consisted of a mixture of fowl plasma, human serum and chick embryo extract. In some cases the serum was from patients with advanced stages of Hodgkin's disease.

The cultures were maintained for a period vary-

ing from a few days to several weeks. After 24 hours incubation, granulocytes, eosinophils, and lymphocytes had migrated from the explant. After 48 hours the outgrowth contained also macrophages, reticulocytes, and fibrocytes. After 48 to 72 hours of incubation there also appeared, on the periphery of the explants large multinucleated giant cells with oval nuclei. The nuclei tended to surround a relatively large, grayish and granular region generally occupying the central portion of the cell. These cells, identified as Sternberg-Reed cells, were found in every case of true Hodgkin's disease and were absent in the other lymphomas and in the normal lymph nodes. The longer the tissue cultures were maintained, the more numerous and larger were these cells.

Brilliant cresyl blue (1:50,000), used as a vital dye for virus cell inclusions, stained the granules of the central body of the Reed-Sternberg cell within 15 minutes after exposure of the culture to the dye. The stained granules were irregular in shape and size. Many appeared to be clumps of smaller granules. The color varied from red to purple of different intensities. The granules of the central body did not stain with Janus B green (1:20,000). Fibrocytes, macrophages, and lymphocytes in the same cultures regularly showed cytoplasmic inclusions within vacuoles, varying in shape and size, which gave the same reddish staining reaction with brilliant cresyl blue as the granules in the central body of the Reed-Sternberg cell. However, cells of the same types obtained from control lymph nodes and grown in a normal medium contained no granules giving the specific coloration with brilliant cresyl blue.

Non-cellular extract of nodes of Hodgkin's disease was obtained from the supernatant fluid of tissue cultures of nodes grown for 14 days and centrifuged at 2000 r.p.m. for half an hour. Fragments of normal lymph nodes were grown for 6 days in a culture medium containing this extract. When vitally stained with brilliant cresyl blue, the lymphocytes and macrophages of these nodes showed cell inclusions within vacuoles of the type found in cultures of nodes of Hodgkin's disease. There was no evidence of giant cells resembling the Reed-Sternberg cells. Control cultures exposed to normal medium did not show the brilliant cresyl blue inclusions.

Supernatant extract from the Hodgkin's disease cultures was injected on to the surface of the chorio-allantoic membrane of 23 hens' eggs which had been incubated for 6 to 11 days. These eggs were incubated for 6 more days and then examined. Eight eggs were found to have vesicles in grape-like clusters measuring about 3 mm. in size. The vesicles contained a clear fluid. As controls, 10 eggs were injected with fluid from normal lymph node cultures and 11 eggs with fluid from lymphosarcoma cultures. None of these showed any lesions.

Portions of the chorio-allantoic membranes containing the lesions produced by the Hodgkin's node extract were grown in tissue cultures for 48 hours and then vitally stained with brilliant cresyl blue. Many of the cells in these cultures showed the specific cell inclusions found in the original tissue cultures of Hodgkin's disease. These inclusions were never found in cultures of chorio-allantoic membranes inoculated with extracts of normal lymph nodes or of lymphosarcomas.

Tissue cultures of all the experiments were fixed every 2 or 3 days, and stained *in toto* with various virus inclusion stains. Of these, Seller's was found to be the best. With this stain only the cell inclusions which color specifically with brilliant cresyl blue took on the red color of the basic fuchsin, while methylene blue colored the nuclei and the usual cytoplasmic granules as well. With the hematoxylin-eosin method, the central zone of the Reed-Sternberg cell proved to be highly basophilic."

Tissue culture studies of inoculated normal cells carried out by Hoster and associates (243, 245) do not confirm the findings of Grand. Hoster and associates point out that inclusion bodies identical with those described by Grand may occur in normal explant cells *in vitro* following the use of so-called "normal" chicken embryo extract and chicken plasma. They suggest that, since the virus of chicken lymphomatosis is a potential contaminant in all chicken flocks, a homologous mammalian tissue substrate and nutriment be used to avoid contamination by this agent.

In addition to dissimilarity in nutriment and substrate, an important difference between Grand's published report (212) and that of Hoster and associates (243, 245) is that Grand's findings are based for the most part on the results of the growth of human Hodgkin's cells in tissue culture while Hoster's findings are based primarily on the inoculation of normal cells in tissue culture with cell-free Hodgkin's material.

Tissue culture studies of normal guinea pig embryo spleen inoculated with cell-free extracts and ultra-centrifuge sediments of Hodgkin's tissue present suggestive changes with respect to cytostimulation and the number of nuclei in giant cells and equivocal or negative findings with respect to inclusion bodies and clot liquefaction. The specificity of these changes in guinea pig cells, however, is both difficult to demonstrate and is subject to theo-

retical objections. Specific investigation of tissue extracts from patients with known virus diseases has not been performed by Hoster and associates.

A more recent trend in the tissue culture studies of Hoster and associates (243) is a comparison study, in roller tube cultures, of (a) normal human cells inoculated biweekly for long periods of time with cell-free Hodgkin's material and (b) uninoculated and inoculated diseased cells obtained from patients with Hodgkin's disease and from control disease sources. Growth of these cells *in vitro* occurs in a human tissue culture medium free of avian constituents.

The nature and significance of a macromolecular particle of virus size observed (in 1945) in electron micrographs of ultra-centrifuge sediments of Hodgkin's tissue extracts is being investigated (243).

REFERENCES

1. Abels, J. C., Kenny, J. M., Craver, L. F., Marinelli, L. O., and Rhoads, C. P. Post-Irradiation Changes in the Levels of Organic Phosphorus in the Blood of Patients with Leukemia. Cancer Research, **1**:771–775. 1941.
2. Abram, J. H. A New Micrococcus, with a Note on the Bacteriology of Lymphadenoma. J. Path. & Bact., **5**:262–264. 1898.
3. Adair, F. E., Craver, L. F., Herrmann, J. B. Hodgkin's Disease of the Breast. Surg., Gynec. & Obst., **80**:205–210. 1945.
4. Aguilar, H. D. Pulmonary Malignant Lymphogranuloma. Semana med., **1**:77–81. 1945.
5. Alexander, T. O. Irradiation Pneumonitis; Report of Case. Bull. Johns Hopkins Hosp., **75**:199–208. 1944.
6. Allan, G. A., and Blacklock, J. W. S. Hodgkin's Disease with Paraplegia. Glasgow M. J., **103**:115–121. 1925.
7. Allen, M., and Mercer, J. O. Spinal Symptoms with Lymphadenoma. J. Neurol. & Psychiat., **17**:1–17. 1936.
8. Amies, C. R. The Particulate Nature of the Agent of Rous Sarcoma No. 1 and of the Fujinami Myxosarcoma. International Congress Microbiol. Rep. II: 99. 1936.
9. Amoss, H. L. Textbook of Medicine by R. L. Cecil. Sixth edition, Philadelphia: W. B. Saunders Co., 1943, p. 234.
10. Apter, L., Hull, E., and Adams, C. C. Maintenance of Sedimentation Rate as a Test for Malignant Disease. Am. J. M. Sc., **206**:168-174. 1943.
11. Arkin, A. Familial Mediastinal Lymphogranuloma. Am. J. M. Sc., **171**:669-682. 1926.
12. Arons, I., and Sokoloff, B. The Role of the Reticulo-Endothelial System in Cancer with Reference to Congo Red Therapy in Roentgen Sickness and Anemia; Preliminary Communication. Am. J. Roentgen., **41**:834-850. 1939.
13. Avent, C. H. Primary Isolated Lymphogranulomatosis (Hodgkin's Disease) of the Stomach; Report of Case. Arch. Surg., **39**:423-428. 1939.
14. Avery, J. W., and Warren, J. W. Unusual Case of Hodgkin's Disease; Preliminary Report. Arch Ophth., **26**:1019–1022. 1941.
15. Avery, J. W., and Warren, J. W. Unusual Case of Hodgkin's Disease; Second Report. Arch. Ophth., **34**:318. 1945.
16. Ayrosa, A. Etiology of Hodgkin's Disease. J.A.M.A., **93**:1574. 1929.
17. Baker, C., and Mann, W. N. Hodgkin's Disease; Study of 65 Cases. Guy's Hospital Rep., **89**:83–107. 1939.
18. Baker, C., and Mann, W. N. Hodgkin's Disease. Lancet, **238-1**:23-25. 1940.
19. Baldridge, C. W., and Awe, C. D. Lymphoma; Study of 150 Cases. Arch. Int. Med., **45**:161–190. 1930.
20. Baldridge, C. W., Rohner, F. J., and Hansmann, G. H. Glandular Fever (Infectious Mononucleosis). Arch Int. Med., **38**:413–448. 1926.
21. Barker, L. F. Severe, Acute Meningo-Encephalopathy of Lymphogranulomatous Origin Occurring in Course of Hodgkin's Disease. Arch. Neurol. and Psychiat., **32**:1038. 1934.
22. Barrett, N. R., and Bond, L. T. Serum Treatment of Hodgkin's Disease, with Account of 4 Cases Treated. Lancet, **231-2**:855-857. 1933.
23. Barron, M. Unique Features of Hodgkin's Disease. Arch. Path., **2**:659-690. 1926.
24. Barron, M. Discussion on "Hodgkin's Disease" by Burnam. J.A.M.A., **87**:1445. 1926.
25. Bateman, O. J., Jr., Squires, G., and Thannhauser, S. J. Hodgkin's Disease Associated with Schilder's Disease. Ann. Int. Med., **22**:426-431. 1945.
26. Beckton, H. On Granules in Cells of Normal Tissues and New Growths. Arch. Middlesex Hosp. (8th Cancer Report), **15**:182-191. 1909.
27. Beebe, G. W. Expected Incidence of Certain Neoplastic Diseases in Veterans. National Research Council Memorandum, issued March, 1947.
28. Behrend, M. Hodgkin's Tumor of Anterior Mediastinum and Anterior Chest Wall. Am. J. Surg., **45**: 348-350. 1939.
29. Bell, E. T. Textbook of Pathology, Third Edition, Philadelphia: Lea and Febiger, 1938, p. 292.
30. Benda, C. Zur Histologie der Pseudoleukämischen Geschwülste. Verhandl. d. deutsch. Gesell., **7**:123-131. 1904.
31. Bennett, R. A. Hodgkin's Diease. Bristol, England: John Wright and Sons, Ltd. 1923.
32. Bercovitz, N. Hodgkin's Disease in Hainan, China. Chinese M. J., **48**:1070-1071. 1934.
33. Bernreiter, M. Hodgkin's Disease Complicated by Brucellosis. J. Kansas M. Soc., **43**:330-333. 1942.
34. Bersack, S. R. Hodgkin's Disease; Pathologic Classification. Am. J. Clin. Path., **13**:253-259. 1943.
35. Bersack, S. R. Hodgkin's Disease—Incidence and Prognosis; Statistical Correlation with the Clinicopathological picture. Arch. Int. Med., **73**:232-237. 1944.
36. Bersack, S. R. Unusual Case of Cutaneous Hodgkin's Disease with Terminal Blood Stream Spread. J.A.M.A., **126**:1025-1026. 1944.
37. Billings, F., and Rosenow, E. C. The Etiology and Vaccine Treatment of Hodgkin's Disease. J.A.M.A., **61**:2122-2123. 1913.
38. Bisson, A. Hodgkin's Disease of Long Duration. J. de Radiol. et d'Electrol., **25**:66-67. 1942.

39. Blau, M., Sinason, H., and Baudisch, O. Radioactivation of Colloidal Gamma Ferric Oxide. Science, **103**:744-748. 1946.
40. Bloomfield, A. L. The Bacterial Flora of Lymphatic Glands. Arch. Int. Med., **16**:197-204. 1915.
41. Bloomfield, A. L. Enlargement of Superficial Lymph Nodes in Brucella Infection. Am. Rev. Tuberc., **45**: 741-750. 1942.
42. Bodansky, M., and Fay, M. Laboratory Manual of Physiological Chemistry, New York: John Wiley and Sons, Inc., 4th ed., p. 274. 1938.
43. Brach, W., Zur Ätiologie und Pathogenese von Pruritis und Prurigo bei Hodgkinscher Lymphogranulomatose. Klin. Wchnschr., **10**:307-308. 1931.
44. Branch, A., Avian Tubercle Bacillus Infection with Special Reference to Mammals and to Man; Its Reported Association with Hodgkin's Disease. Am. J. Path., **12**:253-274. 1931.
45. Branch, C. F. A Case of Congenital Lymphoblastoma. Am. J. Path., **9**:777-780. 1933.
46. Brandt, M. Beitrag zur Pathologischen Anatomie der Lymphogranulomatose. Virchows Arch. f. path. Anat., **272**:400-410. 1929.
47. Brown, I. W., Forbus, W. D., and Kerby, G. P. The Reaction of the Reticuloendothelial System in Experimental and Naturally Acquired Brucellosis of Swine. Am. J. Path., **21**:205-222. 1945.
48. Brunschwig, A., and Kandel, E. A Correlation of Histologic Changes and Clinical Symptoms in Irradiated Hodgkin's Disease and Lymphoblastoma Lymph Nodes. Radiology, **23**:315-326. 1934.
49. Bunting, C. H. Blood Platelets and Megakaryocytes in Hodgkin's Disease. Bull. Johns Hopkins Hosp., **22**: 114-116. 1911.
50. Bunting, C. H. The Blood Picture in Hodgkin's Disease. Bull. Johns Hopkins Hosp., **22**:369. 1911. Ibid, **25**:173. 1914.
51. Bunting, C. H. Hodgkin's Disease. Bull. Johns Hopkins Hosp., **25**:177-180. 1914.
52. Bunting, C. H., and Yates, J. L. An Etiologic Study of Hodgkin's Disease. J.A.M.A., **61**:1803-1804. 1913.
53. Bunting, C. H., and Yates, J. L. Cultural Results in Hodgkin's Disease. Arch. Int. Med., **12**:236-242. 1913.
54. Bunting, C. H., and Yates, J. L. An Etiologic Study of Hodgkin's Disease. J.A.M.A., **62**:516. 1914.
55. Bunting, C. H., and Yates, J. L. Bacteriologic Results in Chronic Leukemia and Pseudoleukemia. Bull. Johns Hopkins Hosp., **26**:376-377. 1915.
56. Bunting, C. H., and Yates, J. L. Similarity of Leukemia, Lymphosarcoma and Hodgkin's Disease. New York Med. J., **104**:1169. 1916.
57. Bunting, C. H., and Yates, J. L. Leukemia, Pseudoleukemia and Hodgkin's Disease. Bull. Johns Hopkins Hosp., **28**:151-153. 1917.
58. Burger, R. E., and Lehman, E. P. Hodgkin's Disease; Review of 54 Cases. Arch. Surg., **43**:839-849. 1941.
59. Burnam, C. F. Hodgkin's Disease. J.A.M.A., **87**: 1445-1452. 1926.
60. Busman, G. J., and Johnston, J. M. Hodgkin's Disease in Dermatologic and General Practice. Pennsylvania M. J., **46**:1153-1156. 1943.
61. Busni, N. Contribution to the Aetiology of the Lymphogranulomatose. Virchows Arch. f. Path. Anat., **268**:614-628. 1928.
62. Cabot. Case 12052. Malignant Lymphoma. Boston M. & S. J., **194**:209-212. 1926.
63. Cabot. Case 12191. Hodgkin's Disease with Terminal Streptococci Septicemia. Boston M. & S. J., **194**: 897-901. 1926.
64. Cabot. Case 12412. X-Ray Therapy of a Case of Hodgkin's Disease with Involvement of the Sternum. Boston M. & S. J., **195**:758-760. 1926.
65. Cabot. Case 25011. Hodgkin's Sarcoma of Stomach, Duodenum and Jejunum. New England J. M., **220**: 31-34. 1939.
66. Cabot. Case 25452. Lymphoblatoma; Hodgkin's Type. New England J. M., **221**:752-754. 1939.
67. Cabot. Case 26062. Hodgkin's Disease of Spleen and Retroperitoneal Tissue. New England J. M., **222**:233-236. 1940.
68. Calvert, E. G. B., and Sanguinetti, H. H. Neoplastic Disease Belonging to the Hodgkin's Group. Lancet, **232-2**:1444-1445. 1934.
69. Cannon, A. B. Practical Points on the Diagnosis and Treatment of the So-Called Lymphoblastoma Group of Diseases. J.M.A. Alabama, **1**:454-467. 1932.
70, Carnett, J. B., Bates, W., and Linney, R. Z. Splenectomy for Hodgkin's Sarcoma and for Epidermal Cyst with Observations Based on Blood Calcium and Blood Platelets. S. Clin. North America **11**:1255-1265. 1931.
71. Carslaw, J. Glycosuria Following X-Ray Therapy; Case of Lymphadenoma. Glasgow M. J., **122**:145-148. 1934.
72. Caspari, W. Betrachtungen über den Krebsproblem besonders vom Standpunkte der Immunität. Ztschr. f. Krebsforsch., **19**:74-100. 1922.
73. Castellanos, A., and Mantero, R. Hodgkin's Disease with Pulmonary Onset in a Child. Bol. Soc. cubana de pediat., **16**:429-446. 1944.
74. Chambers, R., Cameron, G., and Kopac, M. J. Neoplasm Studies. XI. The Effects in Tissue Culture of N,N,N′,N′,-Tetramethyl-*o*-phenylenediamine and Other Compounds on Malignant Lymph Nodes. Cancer Research, **3**:293-295. 1943.
75. Chapman, E. M. Hodgkin's Disease; Negative Skir Reactions to Gland Extracts. Proc. Soc. Exper. Biol & Med., **31**:575-576. 1934.
76. Chapman, E. M. Studies in Hodgkin's Disease; Unsuccessful Experiments to Transmit Hodgkin's Disease to Dogs by Intralymphatic Injection. Proc. Soc. Exper. Biol. & Med., **33**:572-573. 1936.
77. Charache, H. Tumors in One of Homologous Twins; Hodgkin's Disease with Primary Skeletal Manifestations. Am. J. Roentgenol., **54**:179-181. 1945.
78. Charache, H. Tumors in One of Homologous Twins; Hodgkin's Disease; Osteogenic Sarcoma. Am. J. Roentgenol., **46**:69-74. 1941.
79. Charache, H. Hodgkin's Disease in Children. New York State J. M., **46**:507-509. 1946.
80. Charr, R., and Wascolonis, A. Pulmonary Lesions in Hodgkin's Disease. J.A.M.A., **116**:2013-2014. 1941.
81. Chevallier, P., and Bernard, J. La Maladie de Hodgkin. Massen et Cie, Paris, 1932.
82. Chiari, H. Cited by Branch, C. F. A Case of Congenital Lymphoblastoma. Am. J. Path., **9**:777-780. 1933.
83. Ch'in, C. T. Note on White Blood Counts in Whooping Cough. Chinese M. J., **58**:98-103. 1940.

84. Ciechanowski, S. Über die Eintrittspforte, den histologischen Entwicklungsgang und die Häufigkeitszunahme der malignen Granulomatose. Virchows Arch. f. Path. Anat., **303**:206-222. 1938.
85. Clarke, J. M. Discussion on Lymphadenoma. Brit. M.J.,**2**:701-709. 1901.
86. Clayton, W., Howard, A. J., and Thomson, D. Treatment of Mustard Gas Burns. Brit. M. J., **1**: 797-799. 1946.
87. Cohen, M. Binocular Papilledema in a Case of Torulosis Associated with Hodgkin's Disease. Arch. Ophth., **32**:477-479. 1944.
88. Cohn, S., and Richter, M. Modern Views of Hodgkin's Disease. M. Rec., **148**:243-246. 1938.
89. Cohnheim, J. A Case of Pseudoleukemia. Virchows Arch. f. path. Anat., **33**:451-454. 1865.
90. Coley, W. B. Further Evidence in Support of the Theory that Hodgkin's Disease Is a Type of Sarcoma. Surg., Gynec., & Obst., **6**:649-656. 1908.
91. Coley, W. B. End Results in Hodgkin's Disease and Lymphosarcoma Treated by Mixed Toxins of Erysipelas and Bacillus Prodigiosus, Alone or Combined with Radiation. Ann. Surg., **88**:641-667. 1928.
92. Conybeare, E. T. Some Features of Hodgkin's Disease. Guy's Hosp. Rep., **83**:53-62. 1933.
93. Cooper, E. L. Hodgkin's Disease; Some Clinical Aspects with Special Reference to Effects upon Hemopoietic Tissues and Nervous System. M. J. Australia, **1**:585-590. 1935.
94. Cope, O., and Rosenfeld, L. The Lymphatic System. Ann. Rev. Physiol., **8**:297-310. 1946.
95. Coronini C. Über das Paltauf-Sternberg'sche Lymphogranulom; mit besonderer Berücksichtigung der Veränderungen des Verdauungschlauches und solcher an der Leberpforte mit und ohne Gelbsucht. Zugleich ein Beitrag über Lymphogranulomatose Gefässveränderungen. Beitr. z. path. Anat. u. z. allg. Path., **80**:405–478. 1928.
96. Craver, L. F. Personal Communication.
97. Craver, L. F. Clinical Manifestations and Treatment of Leukemia. Am. J. Cancer, **26**:124-136. 1936.
98. Craver, L. F. Some Aspects of Modern Cancer Therapy. Canad. M. A. J., **36**:464-469. 1937.
99. Craver, L. F. Local and General Irradiation in Hodgkin's Disease. Radiology, **31**:42-47. 1938.
100. Craver, L. F. Irradiation in the Lymphomatoid Diseases. Bull. N. Y. Acad. Med., **15**:442-455. 1939.
101. Craver, L. F. Lymphomas and Leukemias. Bull. N. Y. Acad. Med., **23**:79-100. 1947.
102. Craver, L. F. at Conferences on Therapy-Cornell Univ. Med. College. Treatment of Hodgkin's Disease. J.A.M.A., **115**:298-299. 1940.
103. Craver, L. F., Braund, R. R., and Tyler, H. Y. Lesions of the Lungs in the Lymphomatoid Diseases. Am. J. Roentgenol., **45**:342-349. 1941.
104. Craver, L. F., and Copeland, M. M. Changes in the Bone in Hodgkin's Granuloma. Arch. Surg., **28**: 1062-1086. 1934.
105. Craver, L. F., and Haagensen, C. D. Note on Occurrence of Herpes Zoster in Hodgkin's Disease, Lymphosarcoma, and Leukemias. Am. J. Cancer, **16**:502. 1932.
106. Craver, L. F., and Herrmann, J. B. Abdominal Lymphogranulomatosis. Am. J. Roentgenol., **55**:165-172. 1946.
107. Craver, L. F., and MacComb, W. S. Irradiation of the Entire Body. New York State J. M., **34**:249-255. 1934.
108. Craver, L. F., and MacComb, W. S. Heublein's Method of Continuous Irradiation of the Entire Body for Generalized Neoplasms. Am. J. Roentgenol., **32**: 654-674. 1934.
109. Craver, L. F., and Sunderland, D. A. Hodgkin's Disease and Carcinoma of the Colon; Mistaken Diagnosis of Carcinoma of Stomach. J.A.M.A., **114**:1623-1625. 1940.
110. Creevy, C. D. Pyrexia in Malignant Nephroma. J.A.M.A., **92**:1256-1260. 1929.
111. Crowe, S. J., and Wislocki, G. B. Experimental Observations on the Suprarenal Glands. Johns Hopkins Hosp. Bull., **25**:287-304. 1914.
112. Cullinan, E. R. Haemotological Observations on Rabbits and Guinea Pigs; with Special Reference to the Effect of Injections of Barber Yeast. Rose Research on Lymphadenoma. Bristol, England: John Wright and Sons, Ltd., 1932, pp. 109-114.
113. Cunningham, W. F. Hodgkin's Disease; a Study of a Series of 25 Cases. Am. J. M. Sc., **150**:868-886. 1915.
114. Cunningham, W. F. Preliminary Report on a Series of Cases of Hodgkin's Disease from the Pathological Laboratory of the Roosevelt Hospital. Roosevelt Hosp., New York Medical and Surgical Reports, **1**: 235-243. 1915.
115. Cunningham, W. F. The Status of Diphtheroids with Special Reference to Hodgkin's Disease. Am. J. M. Sc., **153**:406-412. 1917.
116. Cunningham, W. F., and McAlpin, K. Experiments with Hodgkin's Disease; Attempt to Produce It in Anthropoids and Other Monkeys. Arch. Int. Med., **32**:353-358. 1923.
117. Custer, R. P., and Bernhard, W. G. Presented before the Pathological Society of Philadelphia. May 8, 1947.
118. Custer, R. P., and Bernhard, W. G. Hodgkin's Disease—Its Relation to Other Neoplasms of Lymphatic Tissue. Abstracts of the Fourth International Cancer Research Congress, St. Louis, Mo., September 2-7, 1947, p. 67.
119. Davenport, L., and Richardson, W. Presentation of a Case: Malignant Lymphoma, Hodgkin's Sarcoma Type. New England J. M., **234**:62-65. 1946.
120. Davidson, M. Practical Notes on Lymphadenoma. Postgraduate M. J., **7**:34-37. 1931.
121. Davies, G. F. S. Hodgkin's Disease. M. J. Australia, **1**:199-212. 1935.
122. Davis, P. L. Personal communication.
123. Davis, P. L. Folic Acid and the Bone Marrow in Radiation Therapy. Am. J. Med., **1**:634–635. 1946.
124. Decker, F. H., Leddy, E. T., and Desjardins, A. U. Leukopenia and Leukocytosis in Lymphoblastoma; Their Reaction to Roentgen Therapy. Am. J. Roentgenol., **39**:747-766. 1938.
125. Delbet, P. Des Hypertrophies Ganglionnaires généralisées; Origine Infectieuse du Lymphadénome Malin. Semaine méd., **13**:430-432. 1893.
126. Delbet, P. Experimental Production of Generalized Hodgkin's Disease in a Dog. Semaine méd., **15**:271. 1895.
127. Desjardins, A. U., and Ford, F. A. Hodgkin's Disease and Lymphosarcoma; Clinical and Statistical Study. J.A.M.A., **81**:925-927. 1923.

128. Desjardins, A. U. Etiology of Lymphoblastoma. J.A.M.A., **103**:1033-1036. 1934.
129. Desjardins, A. U. Problems in Roentgen Therapy for Hodgkin's Disease and Lymphosarcoma. Radiology, **39**:16-26. 1942.
130. Desjardins, A. U. Salient Factors in the Treatment of Hodgkin's Disease and Lymphosarcoma with Roentgen Rays. Am. J. Roentgenol., **54**:707-722. 1945.
131. Desjardins, A. U. Roentgen Treatment for Hodgkin's Disease and Lymphosarcoma of the Chest. Dis. of Chest, **11**:565-589. 1945.
132. Dickey, J. W., Jr., and Forbus, W. D. Chemotactic Properties of Brucella suis; Study of Phagocytosis of Brucella *in vitro* by Normal Nonimmune Human Leukocytes. Am. J. Path., **21**:195-203. 1945.
133. Dietrich, A. Über die Beziehungen der Malignen Lymphome zur Tuberkulose. Beitr. z. klin. Chir., **16**: 377. 1896.
134. Doerr, R., and Berger, W. Der Gehalt des Blutserums an artspezifischen Eiweiss. Ztschr. f. Hyg. u. Infekionskr., **93**:147-162. 1921.
135. Doub, H. P., and Hartman, F. W. Lymphocytic, Myelocytic, and Monocytic Neoplasms; Roentgen Diagnosis and Treatment. J.A.M.A., **105**:942-948. 1935.
136. Dougherty, J. F., and White, A. Effect of Pituitary Adrenotropic Hormone on Lymphoid Tissue. Proc. Soc. Exper. Biol. & Med., **53**:132-133. 1943.
137. Dougherty, J. F., and White, A. Influence of Hormones on Lymphoid Tissue, Structure and Function. The Role of the Pituitary Adrenotropic Hormones in the Regulation of the Lymphocytes and Other Cellular Elements of the Blood. Endocrinology, **35**:1-14. 1944.
138. Dreschfeld, J. Clinical Lecture on Acute Hodgkin's (or Pseudoleucocythemia). Brit. M. J., **1**:893-896. 1892.
139. Dresser, R., and Spencer, J. Hodgkin's Disease and Allied Conditions of Bone. Am. J. Roentgenol., **36**: 809-815. 1936.
140. Duran-Reynals, F. Virus Variation in Relation to the Cancer Problem. Trans. New York Acad. Sc., **8**: 200. 1946.
141. Dziemian, A. J. The Effects of Body-Gassing with Mustard Vapor on the Carbohydrate Metabolism of Dogs. Fed. Proc., **5**:175. 1946.
142. Eagle, H., Magnuson, H. J., and Fleischman, R. BAL as a Specific Detoxifying Agent for Aresenic. Fed. Proc., **5**:175. 1946.
143. Edward, D. G. F. Observations on the Cellular Basis of the Gordon Test for Lymphadenoma. Lancet, **234**:936-938. 1938.
144. Edward, D. G. F. Observations on the Nature of Gordon's Encephalitogenic Agent. J. Path. and Bact., **47**:481-487. 1938.
145. Epstein, E. Sex as a Factor in Prognosis of Hodgkin's Disease. Am. J. Cancer, **35**:230-233. 1939.
146. Erxleben, H., and Herken, R. Steriochemical Analysis of Proteins of Lymphogranuloma and Other Pathologic Tissues. Ztschr f. physiol. chem., **264**: 240-250. 1940. As abstracted by Chemical Abstract No. 797. 1941.
147. Ewing, J. Neoplastic Diseases. Philadelphia: W. B. Saunders Co., p. 407. 1928.
148. Ewing, J. Tissue Reactions to Radiation-Caldwell Lecture. Am. J. Roentgenol., **15**:93-115. 1926.
149. Fabian, E. Die Lymphogranulomatosis (Paltauf-Sternberg). Centralb. f. Allg. Path. u. path. Anat., **22**:145-186. 1911.
150. Falconer, E. H., and Leonard, M. E. Pulmonary Involvement in Lymphosarcoma and Lymphatic Leukemia. Am. J. M. Sc., **195**:294-301. 1938.
151. Faure-Beaulieu, M., and Brun, C. Reserches Expérimentales sur la Granulomatose Maligne. Pouvoir Pathogène des Germes Isolés par Culture. Compt. rend. Soc. de biol., **113**:601-604. 1933.
152. Feldman, H. Maintenance of Sedimentation Rate of Erythrocytes in Cases of Hodgkin's Disease. Am. J. M. Sc., **200**:820-825. 1940.

152a. Feldman, Wm. H. Neoplasms of Domesticated Animals. Philadelphia: W. B. Saunders Co. 1932.

153. Finkelstein, W. Unusual Case of Hodgkin's Disease. Connecticut M. J., **5**:687-688. 1941.
154. Fischer, F. Ueber Malignes Lymphom. Arch f. klin. Chir., **55**:467-472. 1897.
155. Fitchett, M. S., and Weidman, F. D. Generalized Torulosis Associated with Hodgkin's Disease. Arch. Path., **18**:225-244. 1934.
156. Fitz-Hugh, T., and Hodes, P. J. Clinical Experience with Radiophosphorus in Treatment of Certain Blood Dyscrasias. Am. J. M. Sc., **204**:662-665. 1942.
157. Flexner, S. The Pathology of Lymphotoxic and Myelotoxic Intoxication. Univ. Pennsylvania M. Bull., **15**:287-295. 1902-1903.
158. Forbus, W. D., and Gunter, J. U. Pathogenicity of Strains of Brucella Obtained from Cases of Hodgkin's Disease. South. M. J., **34**:376-389. 1941.
159. Forbus, W. D. Studies on Hodgkin's Disease and Its Relation to Infection by Brucella. Am. J. Path., **18**: 745-748. 1942.
160. Forbus, W. D., and Davis, C. L. A Chronic Granulomatous Disease of Swine with Striking Resemblance to Hodgkin's Disease. Am. J. Path., **22**:35-37. 1946.
161. Fox, H. Studies in Diphtheroids. Arch. Int. Med., **16**:465-480. 1915.
162. Fox, H. Lymphogranulomatosis of the Skin in Hodgkin's Disease. Arch Derm. & Syph., **2**:578-593. 1920.
163. Fox, H. Remarks on the Presentation of Microscopic Preparations Made from Some of the Original Tissue Described by T. Hodgkin, 1832. Ann. M. Hist., **8**:370-374. 1926.
164. Fox, H., and Farley, D. L. A Discussion on Effects of X-Ray on Adenopathies. J. Cancer Research, **8**: 162-172. 1924.
165. Fox, H. Polymorphonuclear Neutrophils in Blood in Lymphadenopathies; Their Relation to Classification and Radiation Treatment. Arch. Path., **5**:267-281. 1928.
166. Fox, H., and Farley, D. L. Effect of X-Ray upon the Histology of the Lymph Nodes in Some Cases of Lymphadenopathy as Found by Adenectomy During Treatment. J. Radiol., **4**:261-267. 1923.
167. Fox, H., and Farley, D. L. Relation of Aleukemic Leukemia, So-called Pseudoleukemia and Malignant Granuloma. Am. J. M. Sc., **163**:313-335. 1922.
168. Fox, H., and Farley, D. L. Classification of Lymph-Gland Enlargements, Based upon Glands Removed for Diagnosis. Am. J. M. Sc., **166**:170-185. 1923.
169. Fraenkel, E. Lymphomatosis Granulomatosa. Handbuch der Speziellen Pathologischen Anatomie und Histologie. Edited by F. Henke and O. Lubarsch. Berlin: Julius Springer. 1926. pp. 349-372.

170. Fraenkel, E., and Much, H. Ueber die Hodgkinsche Krankheit (Lymphomatosis Granulomatose). Ztschr. f. Hyg. u. Infektionskr., **67**:159-200. 1910.
171. Fraser, J., and Mekie, E. C. A Study of Lymphogranulomata. Edinburgh M. J., **40**:455-481. 1933.
172. Frawley, J. M. Study of the Virus Factor in Whooping Cough. J. Pediat., **16**:18-20. 1940.
173. Freeman, H. E. Hodgkin's Disease. Arch. Derm. & Syph., **53**:431. 1946.
174. Freifeld, S. E. Lymphoblastoma of the Kidney. Radiology, **46**:507-510. 1946.
175. Freund, H. Studien zur unspezifischen Reiztherapie. Arch. f. Exper. Path. u. Pharmakol., **91**:272-302. 1921.
176. Friedemann, U., and Elkeles, A. Studies on the Aetiology of Blood Diseases. A Pathogenic Agent in Normal Bone Marrow. Brit. M. J., **2**:1110-1112. 1933.
177. Friedemann, U. The Pathogenic Agent in Normal Human Bone Marrow; Its Nature and Relationship to the Lymphadenoma Agent of Gordon. Brit. M. J., **1**:517-518. 1934.
178. Friedman, L. J. Hodgkin's Disease. Radiology, **33**: 354-356. 1939.
179. Funke, J. Malignant Lymphoma. J.M.A. Georgia, **35**:120-121. 1946.
180. Furth, J. Viruses in the Aetiology of New Growths. International Congress Microbiol. Rep. II: 95. 1936.
181. Gall, E. A., and Mallory, T. B. Malignant Lymphoma. Arch. Path., **18**:381-415. 1942.
182. Gall, E. A., and Page, S. G., Jr. Intermittent Fever With Lesions Simulating Those of Hodgkin's Disease; a Case Report. Am. J. Clin. Path., **15**:431-445. 1945.
183. Garvin, C. F. Hodgkin's Disease of Heart and Pericardium. J.A.M.A., **117**:1876-1877. 1941.
184. Galloway, J. Hodgkin's Disease. Brit. M. J., **2**: 1201-1204. 1922.
185. Gambrell, E., and Kracke, R. R. Discussion to Forbus and Gunter (Pathogenicity of Strains of Brucella Obtained from Cases of Hodgkin's Disease). South. M. J., **34**:398. 1941.
186. Gardner, W. U., Kirschbaum, A., and Strong, L. C. Lymphoid Tumors in Mice Receiving Estrogens. Arch. Path., **29**:1-7. 1940.
187. Gardner, W. U., Dougherty, T. F., and Williams, W. L. Lymphoid Tumors in Mice Receiving Steroid Hormones. Cancer Research, **4**:73-87. 1944.
188. Garrod, L. P. A Comparison of the Yeasts Cultivated from Hodgkin's Disease with Similar Organisms from Other Sources. Further Cultural Observations. Rose Research on Lymphadenoma. Bristol: John Wright & Sons, Ltd. 1932. pp. 95-106.
189. Gemmell, A. Menstruation and Pregnancy in Hodgkin's Disease. J. Obst. and Gyn. Brit. Emp., **30**:373-381. 1923.
190. Gemmell, A. Menstruation and Pregnancy in Hodgkin's Disease. Lancet, **204**:543-544. 1923.
191. Gibbons, H. W. The Relation of Hodgkin's Disease to Lymphosarcoma. Am. J. M. Sc., **133**:692-705. 1906.
192. Gilbert, R. Radiotherapy in Hodgkin's Disease. Am. J. Roentgenol., **41**:198-241. 1939.
193. Gilman, A., and Philips, F. S. Biological Actions and Therapeutic Applications of B-Chloroethyl Amines and Sulfides. Science, **103**:409-415. 1946.
194. Ginsburg, S. Lymphosarcoma and Hodgkin's Disease; Biological Characteristics. Ann. Int. Med., **8**: 14-36. 1934.
195. Ginsburg, S. Hodgkin's Disease with Predominant Localization in the Nervous System. Arch. Int. Med., **39**:571-595. 1927.
196. Ginzler, A. M. The Effect of BAL Therapy on the Renal Lesion in Mercury Poisoning. Fed. Proc., **5**: 221. 1946.
197. Glazebrook, A. J., and Tomaszewski, W. Ichthyosiform Atrophy of Skin in Hodgkin's Disease; Report of Case with Reference to Vitamin A Metabolism. Arch. Dermat. & Syph., **50**:85-89. 1944.
198. Goldmann, E. E. Beitrag zu der Lehre von dem "Malignen Lymphom." Centralbl f. Allg. Path. u. path. Anat., **3**:665-680. 1892.
199. Goldman, L. B. Hodgkin's Disease; Analysis of 212 Cases. J.A.M.A., **114**:1611-1616. 1940.
200. Goldman, L. B., and Victor, A. W. Hodgkin's Disease; Salient Clinical Features and Relative Value of Various Methods of Treatment Based upon Study of 319 Cases. New York State J. M., **45**:1313–1318. 1945.
201. Goodman, L. S., Wintrobe, M. M., McLennan, M. T., Dameshek, W., Goodman, M. J., and Gilman, A. Use of Methyl-Bis (B chloroethyl) Amine Hydrochloride and Tris (B Chloroethyl) Amine Hydrochloride (Nitrogen Mustards) in the Therapy of Hodgkin's Disease, Lymphosarcoma, Leukemia and Certain Allied and Miscellaneous Disorders. Approaches to Tumor Chemotherapy. Washington, D. C.: A.A.A.S. 1947. pp. 338-346.
202. Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., Gilman, A., and McLennan, M. T. Nitrogen Mustard Therapy. J.A.M.A., **132**:126-132. 1946.
203. Goodrich, M. E. Preliminary Observations Concerning Effects of Roentgen Irradiation in Presence of Fluorescein. Am. J. Roentgenol., **34**:378-380. 1935.
204. Gordon, M. H. The Problem of the Aetiology of Hodgkin's Disease. St. Barth. Hosp. Rep., **63**:69-75. 1930.
205. Gordon, M. H. "Studies on Aetiology of Lymphadenoma." Rose Research on Lymphadenoma. Bristol, England: John Wright and Sons, Ltd. 1932, pp. 7-76.
206. Gordon, M. H. Remarks on Hodgkin's Disease; Pathogenic Agent in Glands, and Its Application in Diagnosis. Brit. M. J., **1**:641-644. 1933.
207. Gordon, M. H. Etiology of Lymphadenoma, Sensitized Vaccine of Elementary Bodies. Lancet, **231**: 65-68. 1936.
208. Gordon, M. H., Gow, A. E., Levitt, W. M., and Weber, F. P. Recent Advances in Pathology and Treatment of Lymphadenoma. Proc. Roy. Soc. Med., **27**:1035-1050. 1934.
209. Gordon, M., Warner, E.C., Robb-Smith, A. H. T., and White, D. Discussion on the Etiology and Diagnosis of Lymphadenoma. Proc. Roy. Soc. Med., **30**: 541-550. 1937.
210. Gowers, Sir W. R. Hodgkin's Disease. Reynold's System of Medicine. **5**:306-352. 1878.
211. Graef, I., Karnofsky, D. A., Jager, V. B., and Smith, H. W. The Clinical and Pathologic Effects of the Vesicant Nitrogen and Sulfur Mustards. Fed. Proc., **5**:221. 1946.

212. Grand, C. G. Tissue Culture Studies of Cytoplasmic Inclusion Bodies in Lymph Nodes of Hodgkin's Disease. Proc. Soc. Exper. Biol. & Med., **56**:229-230. 1944.
213. Gray, R. C., Baker, A. B., Cottrell, L., and Skogland, J. E. Hodgkin's Disease of Central Nervous System. Internat. Clin., **4**:230-236. 1941.
214. Green, R. G., and Stulberg, C. S. Cell-Blockade in Canine Distemper. Proc. Soc. Exper. Biol. & Med., **61**:117-121. 1946.
215. Green, R. G., and Stulberg, C. S. Distemperoid Virus Interference in Canine Distemper. Science, **103**: 497-498. 1946.
216. Greenfield, W. S. Specimens Illustrative of the Pathology of Lymphadenoma and Leucocythaemia. Tr. Path. Soc. London, **29**:272-304. 1878.
217. Grossman, E. B. Abdominal Hodgkin's Disease. No Superficial Lymph Node Enlargement. Macrocytic Anemia Resistant to Liver Therapy. J. Mt. Sinai Hosp., **10**:804-806. 1944.
218. Grosz, S. Über eine bisher nicht beschriebene Hauterkrankung (Lymphogranulomatosis cutis). Beitr. z. Path. Anat., **39**:405–430. 1906.
219. Gruber, G. B. Lymphogranulomatose der Bauchspeicheldruse. Handbuch der Speziellen Pathologischen Anatomie und Histologie Vol. 5, Pt. 2, p. 431-435, Edited by Henke and Lubarsch, Julius Springer, Berlin. 1929.
220. Guerriero, H. E. Four Cases of Hodgkin's Disease Treated with Radium. New Orleans M. & S. J., **83**: 698-705. 1931.
221. Haden, R. L., and Burns, J. T. Hodgkin's Disease; A Review of 47 Cases. Cleveland Clin. Quart., **9**: 144-146. 1942.
222. Hahn, P. F., and Sheppard, C. W. Selective Radiation Obtained by the Intravenous Administration of Colloidal Radioactive Isotopes in Diseases of the Lymphoid System. South. M. J., **39**:558-562. 1946.
223. Halliday, N., and Weiss, C. Effect of Biotin and Other B Vitamins on Proteinases. Fed. Proc., **5**:223. 1946.
224. Hammond, A. E. Perforation of Trachea by Mediastinal Tumor (Hodgkin's Disease). Ann. Otol., Rhin., & Laryng., **50**:929-935. 1941.
225. Handel, M., and Tadenuma, K. The Metabolism of Carcinomatous Rats as Influenced by Roentgen Radiation of the Tumor. Deutsche med. Wchnschr., **1**:271. 1924.
226. Hanrahan, E. M., Jr. Results of Treatment by Autogenous Gland Filtrate in Hodgkin's Disease. Ann. Surg., **92**:23-34. 1930.
227. Harrell, G. T. Hodgkin's Disease with Invasion of Pericardium and Gall Bladder; Review of Literature and Report of Case with Autopsy. Arch. Path., **28**: 58-64. 1939.
228. Haythorn, S. R. Multinucleated Giant Cells. Arch Path., **7**:651-713. 1929.
229. Haythorn, S. R., Robinson, G. H., and Johnson, L. Report of Case of Early Hodgkin's Disease Secondarily Infected with a Strain of Pathogenic Monilia. Ann. Int. Med., **6**:72-87. 1932.
230. Heacock, C. M. Hodgkin's Disease. Memphis M. J., **20**:82-88. 1945.
231. Heilman, F. R., and Kendall, E. C. Influence of 11-Dehydro-17-Hydroxycorticosterone (Compound E) on Growth of a Malignant Mouse Tumor. Endocrinology, **34**:416-420. 1944.
232. Hemplemann, L. A., Reinhard, E. H., Moore, C. V., Bierbaum, O. S., and Moore, S. Hematologic Complications of Therapy with Radioactive Phosphorous. J. Lab. & Clin. Med., **29**:1020-1041. 1944.
233. Hendrick, A. C., and Burton, E. F. Case of Hodgkin's Disease Treated with Colloidal Elemental Arsenic. Canad. M.A.J., **36**:519-520. 1937.
234. Herbut, P. A., Miller, F. R., and Erf, L. A. Relation of Hodgkin's Disease, Lymphosarcoma, and Reticulum Cell Sarcoma. Am. J. Path., **21**:233-253. 1945.
235. Herschler, H., and Stein, J. J. Osteopetrosis Associated with Hodgkin's Disease; Review of Literature and Report of Case. Am. J. Roentgenol., **43**:74-80. 1940.
236. Hickey, E. The Present State of Our Knowledge with Regard to Hodgkin's Disease. Ulster M. J., **5**: 101-106. 1936.
237. Higley, C. B., and Hauser, H. Diagnosis, Prognosis, and Treatment of Hodgkin's Disease. Ohio State M. J., **35**:1075-1079. 1939.
238. Hinsdale, G. Case of Lymphadenoma. Hodgkin's Disease. Pam. 9 of Medical Papers by Hinsdale, 1883. (Extracted from Medical News, 1886, Volume 49)
239. Hodgkin, T. On Some Morbid Appearances of the Absorbent Glands and Spleen. Med.-Chir. Trans., **17**: 68-114. 1832.
240. Holt, L. E., and McIntosh, R. Diseases of Infancy and Childhood. Eleventh edition. New York: D. Appleton-Century Co. 1939, p. 672.
241. Holthusen, H. Die Wirkung der Röntgenstrahlen in biolagischer Hinsicht. Strahlentherapie, **18**:241-262. 1924.
242. Horder, T. A Clinical Concept of Lymphadenoma or Hodgkin's Disease. Rose Research on Lymphadenoma. Bristol, England: John Wright and Sons, Ltd., 1932, pp. 1-6.
243. Hoster, H. A. Personal communication.
244. Hoster, H. A. Studies in Hodgkin's Syndrome; A Distribution Study of Hodgkin's Disease in the United States. Ohio J. Sc., **44**:245-250. 1944.
245. Hoster, H. A., Riddle, J. W., Heise, M. D., Flower, M. S., Rieman, M. S., Shanley, M. E., Welshimer, B. J., and Doan, C. A. Studies in Hodgkin's Syndrome. VI. Clinical and Etiologic Studies. Ohio State M. J., **43**:721-724. 1947.
246. Hoster, H. A. Studies in Hodgkin's Syndrome. Etiologic Studies in Hodgkin's Disease. Abstr., A.A.A.S. Gibson Island Cancer Conference, August 13, 1946. Cancer Research, **7**:48. 1947.
247. Hoster, H. A., Doan, C. A., and Schumacher, M. Studies in Hodgkin's Syndrome; Search for Brucella in Hodgkin's Syndrome. Proc. Soc. Exper. Biol. & Med., **57**:86-88. 1944.
248. Hoster, H. A., and Doan, C. A. Studies in Hodgkin's Syndrome; Therapeutic Use of Radioactive Phosphorous. J. Lab. & Clin. Med., **30**:678-683. 1945.
249. Hoster, H. A., Doan, C. A., and Schumacher, M. Studies in Hodgkin's Syndrome; Relationship of Tubercle Bacilli to Hodgkin's Syndrome. J. Lab. & Clin. Med., **30**:675-677. 1945.
250. Hoster, H. A., and Bechtel, W. R. Personal Communication Based on Work by Hoster and Bechtel presented in a Thesis for the Degree of M. Sc. by W. R. Bechtel at Ohio State University Depts. of Medicine and Bacteriology, 1946.

251. Hoster, H. A., and Zanes, R. P., Jr. Personal communication.
252. Hoster, M. S. Serologic Studies of Hodgkin's Disease. Master's Thesis, Ohio State University, Columbus, Ohio. 1947.
253. Howells, L. Tuberculous Splenomegaly. Brit. J. Tuberc., **33**:178-187. 1939.
254. Hoyt, L. H. Study of Gordon Test for Hodgkin's Disease. J. Iowa State M. Soc., **29**:394-397. 1939.
255. Hughes, C. W., and Job, T. T. Attempt to Involute Completely All of Lymphoid Tissue of Albino Rat by X-Rays. Radiology, **29**:194-201. 1937.
256. Hurdin, B. L., Jr. A Case of Hodgkin's Disease with Massive Collapse and Cavitation of the Lung. Am. J. M. Sc., **197**:92-99. 1939.
257. Isaacs, R. Hodgkin's Disease. M. Clin. North America, **28**:201-213. 1944.
258. Jackson. H., Jr. The Classification and Prognosis of Hodgkin's Disease and Allied Disorders. Surg., Gynec., & Obst., **64**:465-467. 1937.
259. Jackson, H., Jr. Hodgkin's Disease and Allied Disorders. New England J. Med., **220**:26-30. 1939.
260. Jackson, H., Jr. Hodgkin's Disease. Bull. New England M. Center, **6**:216-218. 1944.
261. Jackson, H., Jr. Hodgkin's Disease and Allied Conditions. Bull. Vancouver M., **21**:269-278. 1945.
262. Jackson, H., Jr., and Parker, F., Jr. Hodgkin's Disease; I. General Considerations. New England J. Med., **230**:1-8. 1944.
263. Jackson, H., Jr., and Parker, F., Jr. Hodgkin's Disease; II. Pathology. New England J. Med., **231**: 35-44. 1944.
264. Jackson, H., Jr., and Parker, F., Jr. Hodgkin's Disease; III. Symptoms and Course. New England J. Med., **231**:636-646. 1944.
265. Jackson, H., Jr., and Parker, F., Jr. Hodgkin's Disease; IV. Involvement of Certain Organs. New England J. Med., **232**:547-559. 1945.
266. Jackson, H., Jr., and Parker, F., Jr. Hodgkin's Disease; V. Involvement of Certain Other Organs. New England J. Med., **233**:369-376. 1945.
267. Jackson, H., Jr., and Parker, F., Jr. Hodgkin's Disease; VI. Clinical Diagnosis. New England J. Med., **234**:37-41. 1946.
268. Jackson, H., Jr., and Parker, F., Jr. Hodgkin's Disease; VII. Treatment and Prognosis. New England J. Med., **234**:103-110. 1946.
269. Jackson, H., Jr., and Parker, F., Jr. Hodgkin's Disease and Allied Disorders. New York: Oxford University Press. 1947, p. 177.
270. Jacobson, L. O., Spurr, C. L., Smith, T. R., and Dick, G. F. Radioactive Phosphorous (P_{32}) and Alkylamines (Nitrogen Mustards) in the Treatment of Neoplastic and Allied Diseases of the Hemopoietic System. M. Clin. North America., 3-18, January, 1947.
271. Jacobson, L. O., Spurr, C. L., Guzman-Barron, E. S., Smith, T., Lushbaugh, C., and Dick, G. F. Nitrogen Mustard Therapy. J.A.M.A., **132**:263-271. 1946.
272. Jacox, H. W., Peirce, C. B., and Hildreth, R. C. Roentgenologic Considerations of Lymphoblastoma. Roentgen Therapy of Hodgkin's Disease. Am. J. Roentgenol., **36**:165-168. 1936.
273. Jenkinson, E. L. Hodgkin's Disease. Radiology, **19**: 41-49. 1932.
274. Jianu, J., and Netta, T. Appearance of a Sarcoma in a Rabbit Following Graft of Lymphogranuloma from Man. Ann. d'Anat. path., **8**:944-951. 1931.
275. Jolly, J. Action des rayons X sur les cellules. Diminution de la réaction d'un organe sensible par la ligature des artères afférentes. Compt. rend.. Soc. biol., **91**:532–534. 1924.
276. Jones, C. M. Discussion in Davenport and Richardson: Presentation of Case. Malignant Lymphoma, Hodgkin's Sarcoma Type. New England J. M., **234**: 65. 1946.
277. Jones, G. W. Historical Review of Hodgkin's Disease with Special Reference to Its Histology and Characteristic Cells. Ann. M. Hist., **2**:471-481. 1940.
278. Kamellin, S. Uveitis Associated with Hodgkin's Disease; Report of Case. Arch. Ophth., **31**:517-519. 1944.
279. Kamellin, S. Fundus Changes in Hodgkin's Disease. Am. J. Ophth., **28**:909. 1945.
280. Kaplan, I. I. Hodgkin's Disease in Childhood. Arch. Pediat., **51**:325-328. 1934.
281. Kaplan, I. I. One Year's Observations of the Treatment of Cancer with Avidin (Egg White). Am. J. M. Sc., **207**:733-743. 1944.
282. Karnofsky, D. A. The Nitrogen Mustards and Their Application in Neoplastic Diseases. N. Y. State J. Med., **47**:992-993. 1947.
283. Karnofsky, D. A., Burchenal, J. H., Ormsbee, R. A., Cornman, I., and Rhoads, C. P. Experimental Observations on the Use of Nitrogen Mustards in the Treatment of Neoplastic Disease. Approaches to Tumor Chemotherapy 293-305, 1947. A.A.A.S., Washington, D. C.
284. Karnofsky, D. A., Craver, L. F., Rhoads, C. P., and Abels, J. C. An Evaluation of Methyl-Bis (B chloroethyl) Amine Hydrochloride and Tris (B chloroethyl) Amine Hydrochloride (Nitrogen Mustards) in the Treatment of Lymphomas, Leukemia and Allied Diseases. Approaches to Tumor Chemotherapy, 319-337, 1947. A.A.A.S., Washington, D. C.
285. Karnofsky, D. A., Parisette, L. M., Patterson, P. A., and Jacquez, J. A. The Behavior and Growth of Homologous and Heterologous Normal and Neoplastic Tissues on the Chick Embryo; and Influence of Various Agents on Tumor Growth. Abstracts of the Fourth International Cancer Research Congress, St. Louis, Mo., September 2-7, 1947.
286. Karsner, H. T. A Study of Cases of Hodgkin's Disease and Certain Allied Conditions. Arch. Int. Med., **6**:175-195. 1910.
287. Karsner, H. T. Human Pathology, Sixth edition. Philadelphia: J. B. Lippincott Co. 1942.
288. Keller, P. D. Clinical Syndrome Following Exposure to Atomic Bomb Explosions. J.A.M.A., **131**:504-506. 1946.
289. Kelsall, M. A. Relationships of Lymphocytes and Cancer. Science, **102**:456-457. 1947.
290. Kelser, R. A., and King, L. Studies of a Paralysis Syndrome Produced in Rabbits and Guinea Pigs by Extracts of Normal Bone Marrow. Am. J. Path., **12**: 317-331. 1936.
291. Kierland, R. R., and Montgomery, R. Cutaneous Ulcerative Hodgkin's Disease. Proc. Staff Meet., Mayo Clin., **16**:124-128. 1941.
292. King, D. P. The Biological Test for Hodgkin's Disease. St. Thomas Hosp. Rep., **3**:68-80. 1938.

293. KINSEY, V. E., and GRANT, W. M. The Reaction of Mustard Gas with Proteins; the Nutritional Value of Casein Reacted with Mustard Gas. Arch. Biochem., **10**:303–309. 1946.
294. KINSEY, V. E., and GRANT, W. M. The Reaction of Mustard Gas with Proteins; Biological Assay of Amino-Acids Affected. Arch. Biochem., **10**:311-320. 1946.
295. KLAWANS, A. H. Pregnancy Complicated by Hodgkin's Disease. Am. J. Obst. & Gynec., **43**:895-896. 1942.
296. KLEMPERER, P. Spleen in Hodgkin's Disease, Lymphosarcomatosis, and Leukemia. Am. J. M. Sc., **188**: 593-596. 1934.
297. KLIMA, R. Ueber Blutbefunde bei Lymphogranulomatose. Wiener Klin. Wchnschr., **44**:445-446. 1931.
298. KNIPPING, H. W., and KOWITZ, H. L. Über die Einwirkung der Röntgenstrahlen auf die Eiweisskorper des Plasmas. Fortschr. a. d. Geb. d. Röntgenstrahlen, **31**:660-664. 1923.
299. KOENIG, E. C., and CULVER, G. J. Two Cases of Hodgkin's Disease Involving the Stomach. Am. J. Roentgenol., **46**:827-831. 1941.
300. KOFOID, C. A., BOYERS, L. M., and SWEZY, O. Occurrence of Endamoeba Dysenteriae in the Lesions of Hodgkin's Disease. J.A.M.A., **78**:1604-1607. 1922.
301. KOFOID, C. A., SWEZY, O. Amebiasis of the Bones. J.A.M.A., **78**:1602-1604. 1922.
302. KOHUT, H. Unusual Involvement of the Nervous System in Generalized Lymphoblastoma. J. Nerv. & Ment. Dis., **103**:9-20. 1946.
303. KOOREMAN, P. J., and HAEX, A. J. Ch. Hodgkin's Disease of the Skeleton. Acta med. Scandinav., **115**: 177-196. 1943.
304. KORANYI. Discussion to Borday: Einfahrungen in der pathologischen Anatomie und Hisopathologie der Lymphogranulomatosis. Klin. Wchnsch., **1**:466. 1930.
305. KOSTER, L. Changes in the Sedimentation Rate in Stored Citrated Blood as a Diagnostic Aid in Malignant Tumors and Lymphogranuloma. Nederl. Tijdschr. v. gennesk, **81**: III, 3668. 1937.
306. KRANTZ, C. I. The Basal Metabolism in Lymphoblastoma. Am. J. M. Sc., **176**:577-587. 1928.
307. KRAVITZ, D. Hodgkin's Disease of the Lid. Arch. Ophth., **21**:844-851. 1939.
308. KRISTJANSON, H. T. Complement-Fixation in Hodgkin's Disease and Allied Affections. Am. J. M. Sc., **156**:720-725. 1918.
309. KRUEGER, F. J., and MEYER, O. O. Lymphogranulomatosis (Hodgkin's Disease); Review of 60 Cases. J. Lab. & Clin. Med., **21**:682-689. 1936.
310. KRUMBHAAR, E. B. Is Typical Hodgkin's Disease Infection or Neoplasm? Am. J. M. Sc., **188**:597-604. 1934.
311. KRUMBHAAR, E. B. Present Status of Hodgkin's Disease. Univ. Wisconsin Symposium on Blood. Madison: University of Wisconsin Press. 1939.
312. KUCZYNSKI, M. H., and HAUCK, G. Pathogenesis of Lymphogranuloma. Ztschr. f. klin. Med., **99**:102-128. 1923.
313. KUNDRAT. Ueber Lymphogranulomatose. Wien. klin. Wchnschr., **6**:211-234. 1893.
314. KUSHNER, J. I. Pregnancy Complicating Hodgkin's Disease (Lymphogranuloma) Am. J. Obst. & Gynec., **42**:536-538. 1941.
315. LANDOLT, R. F. Lymphogranulomatosis Associated with Acute Hemorrhagic Pancreatitis. Klin. Wochnschr., **22**:36. 1943.
316. LANG, F. J. Experimentelle Untersuchungen über die Histogenese der extramedullären Myelopoese. Ztschr. f. mikr-anat. Forsch., **4**:417-447. 1926.
317. LANGER, H. New Technique for Myeloid and Lymphatic Leucemia, Polycythemia Rubra Vera and Hodgkin's Disease; Roentgen Therapy in Hyperplastic Blood Dyscrasias. Am. J. Roentgenol., **34**:214-233. 1935.
318. LANGHANS, T. Das Maligne Lymphosarkom (Pseudoleukemie). Virchows Arch. f. path. Anat., **54**:509-537. 1872.
319. LAURENCE, W. L. Induced Biotin Deficiency as Possible Explanation of Observed Spontaneous Recessions in Malignancy. Science, **94**:88-89. 1941.
320. LEMON, W. S. Tuberculosis as an Etiologic Factor in Hodgkin's Disease. A Historical Review. Am. J. M. Sc., **127**:178-188. 1924.
321. L'ESPERANCE E. Experimental Inoculation of Chickens with Hodgkin's Nodes. J. Immunol., **16**:37-60. 1929.
322. L'ESPERANCE, E. S. Studies in Hodgkin's Disease. Ann. Surg., **93**:162-168. 1931.
323. LEVIN, I. Lymphoma Malignum (Hodgkin's Disease) and Lymphosarcoma. J.A.M.A., **96**:421-426. 1931.
324. LEVIN, O. L., and BEHRMAN, H. T. Hodgkin's Disease of the Skin. J. Mt. Sinai Hosp., **11**:207-210. 1944.
325. LEVITT, A., and WEISMAN, S. J. Hodgkin's Disease: Case Series Analysis. M. Times, **68**:315-318. 1940.
326. LEVY, S. Hodgkin's Disease; Report of a Case of Mediastinal Type with Leukopenia and Terminal Atelectasis. New England J. Med., **233**:322-325. 1945.
327. LEWIS, M. R. The Behavior of Dorothy Reed Cells in Tissue Cultures. Am. J. M. Sc., **201**:467. 1941.
328. LICHTENSTEIN, A. Untersuchungen über die Aetologie der Lymphogranulomatosis. Frankfurt. Ztschr. f. path., **24**:529-635. 1921.
329. LINCOLN, M. Hodgkin's Disease with Eosinophilia; Report of a Case with Autopsy. Boston M. & S. J., **158**:677-681. 1908.
330. LIMPER, M. A. Hodgkin's Disease in Childhood. Kentucky M. J., **37**:97-102. 1939.
331. LINN, F. D. Laryngeal Manifestations in a Case of Hodgkin's Disease. Memphis M. J., **15**:210. 1940.
332. LISA, J. R. Neurologic Complications in Hodgkin's Disease. New York State J. M., **40**:62-63. 1940.
333. LITTERER, W. Corynebacterium Hodgkini. J.A.M.A., **62**: 1498. 1914.
334. LONGCOPE, W. T. On the Pathological Histology of Hodgkin's Disease, with a Report of a Series of Cases. Bull. Ayer Clin. Lab., Pennsylvania Hosp., **1**: 1-76. 1903.
335. LONGCOPE, W. T. Notes on the Experimental Inoculation of Monkeys with Glands from Cases of Hodgkin's Disease. Bull. Ayer Clin. Lab., Pennsylvania Hosp., **4**:18-21. 1907.
336. LONGCOPE, W. T., and MCALPIN, K. R. Hodgkin's Disease. Cecil's Text-Book of Medicine, Sixth edition. Philadelphia: W. B. Saunders Company. 1943, p. 1010.
337. LONGCOPE, W. T., and MCALPIN, K. R. Hodgkin's Disease. Oxford Medicine, **4**, part 1, 1-43. 1920.

338. Loseke, L., and Craver, L. F. Diagnosis of Hodgkin's Disease by Aspiration Biopsy. Blood, **1**:76-82. 1946.
339. Low-Beer, B. V. A., Lawrence, J. H., and Stone, R. S. Therapeutic Use of Artificially Produced Radioactive Substances; Radiophosphorus, Radiostrontium, Radioiodine, with Special Reference to Leukemia and Allied Disease. Radiology, **39**:573-597. 1942.
340. Lubarsch, O. Über Lymphogranulomatose. Berl. klin. Wchnschr., **55**:708-710. 1918.
341. Luden, G. Studies on Cholesterol. J. Lab. & Clin. Med., **3**:141. 1917.
342. Luden, G. Remarks on Effect of X-Ray on Adenopathies. J. Cancer Research, **8**;167. 1924.
343. MacCormac, H. Mycosis fungoides Treated by Malaria, Terminating in Hodgkin's Disease. Brit. M. J., **2**:645-646. 1941.
344. MacKenzie, I., and van Rooyen, C. E. Relation of Jochmann's and Other Enzymes to Encephalitogenic Agent in Lymphadenomatous Lymphatic Glands. Brit. M. J., **1**:406-411. 1935.
345. MacMahon, H. E. Case of Hodgkin's Disease in Dog. Am. J. Path., **10**:309-312. 1934.
346. MacMahon, H. E., and Parker, F., Jr. Case of Lymphoblastoma, Hodgkin's Disease and Tuberculosis. Am. J. Path., **6**:367-380. 1930.
347. MacNalty, A. S. Lymphadenoma with Relapsing Fever. Quart. J. Med., **5**:58-108. 1911.
348. Magrini, A., and Menghini, G. The Iodine Number in Malignant Lymphogranuloma. Klin. Wchnschr., **20**:1010. 1941. Chem. Abst., 5475. 1943.
349. Mahnert, A. Glycolysis by Cancer Cells. Wien. klin. Wchnschr., **37**:1114-1115. 1924.
350. Major, R. H., and Leger, L. H. Marked Eosinophilia in Hodgkin's Disease. J.A.M.A., **112**:2601-2602. 1939.
351. Malisoff, W. M. Personal communication.
352. Mallory, F. B. Principles of Pathologic Histology. Philadelphia and London: W. B. Saunders Co. 1914, pp. 677-681.
353. Malpighi, De Viscerum Structura, Bonn, Opera Omnia, **2**:111. 1666.
354. Mankin, Z. W. Klinik, Diagnostik und Pathologische Anatomie der Lymphogranulomatose auf Grund des Materials des Onkologischen Instituts. Arch. f. klin. Chir., **176**:744-800. 1933.
355. Manson, M. H. Biological Phenomena in Hodgkin's Disease. Minnesota Med., **18**:263-265. 1935.
356. Marcellus, M. B. Hodgkin's Disease with Herpes Zoster and Varicella. Northwest Med., **38**:279-282. 1939.
357. Marine, D., and Rosen, S. H. Sex Hormones and Lymphomatosis in Fowls. Proc. Soc. Exper. Biol. & Med., **47**:61-62. 1941.
358. Markowitz, B. Theories of Mycosis Fungoides, Hodgkin's Disease, etc. with 2 Case Reports. Am. J. Surg., **16**:113-117. 1932.
359. Marshall, M. A Case of Acute Miliary Tuberculosis Showing the Blood Picture of Acute Myelogenous Leukemia. Arch. Int. Med., **16**:1045-1054. 1915.
360. Martin, C. F. Leukemia and Hodgkin's Disease, from Forchheimer's Therapeuses of Internal Disease, Vol. 3, 844-857. 1913.
361. Martinolli, A. Sull' Eziologia della linfogranulomatosi maligna. Arch. di path. e. clin. med., **8**:395-407. 1929.
362. Mascheroni, H. A., Ruessi, C., and Clerici, L. E. Chronic Stenosis of Jejunoileum Due to Intestinal Lymphogranulomatosis. Arch. Argent. de enferm. d. ap. digest. y de la nutricion, **19**:466-478. 1944.
363. Mawson, C. A. Viruses and Virus Diseases, Virus Causation of Animal Tumors. Rep. II. International Congress Microbiol., **102**, 1936.
364. Maximov, A. A., and Bloom, W. A Textbook of Histology. Philadelphia: W. B. Saunders Co. 1944, pp. 98-116.
365. Mayr, J. K., and Moncorps, C. Eosinophilie und Milz. Münchener med. Wchnschr., **73**:1777–1782. 1926.
366. McAlpin, K. R. Blood Count in Hodgkin's Disease; Report of Cases. Arch. Int. Med., **32**:954-957. 1923.
367. McCausland, D. J. M. Hodgkin's Disease in Children. Arch. Dis. Child., **16**:59-62. 1941.
368. McGrath, J. Hodgkin's Disease. Irish J. Med. Sc., 643-666. 1933.
369. McHeffey, G. J., and Petersen, R. F. Hodgkin's Disease Occurring Simultaneously in Two Brothers. J.A.M.A., **102**:521-522. 1934.
370. McJunkin, F. A. Histologic Resemblance of the Rous Chicken Sarcoma No. 1 to Hodgkin's Granuloma. J. Cancer Research, **12**:47-52. 1928.
371. McNaught, J. B. The Gordon Test for Hodgkin's Disease. A Reaction to Eosinophils. J.A.M.A., 111: 1280-1284. 1938.
372. Medinger, F. G., and Craver, L. F. Total Body Irradiation, with a Review of Cases. Am. J. Roentgenol., **48**:651-671. 1942.
373. Medlar, E. M. Avian Tuberculosis in Normal and Vaccinated Rabbits. Am. J. Path., **7**:475-490. 1931.
374. Medlar, E. M. Interpretation of the Nature of Hodgkin's Disease. Am. J. Path., **7**:499-514. 1931.
375. Medlar, E. M., and Sasano, K. T. Significance of Lesions Resembling Hodgkin's Disease in Tuberculosis. Am. J. Path., **7**:491-498. 1931.
376. Medlar, E. M., and Sasano, K. T. Interpretation of the Nature of Hodgkin's Disease; Report of Neoplasm in Rabbit which Corresponds Closely to Hodgkin's Disease in Man. Am. J. Cancer, **29**:102-110. 1937.
377. Mellon, R. R. Cultural and Vaccine Results in a Case of Hodgkin's Disease. Am. J. M. Sc., **150**:245-258. 1915.
378. Mendel, D. L., and Korenberg, M. Maintenance of Sedimentation Rate of Erythrocytes in Cases of Cancer, Hodgkin's Disease, and Leukemia. Canad. M. A. J., **51**:353-355. 1944.
379. Mendiola, R. Histopathology of Hodgkin's Disease. Arch. Med., Mex., **2**:543-563. 1944.
380. Meyer, O. O. Some Therapeutic Experiences with Hodgkin's Disease. J.A.M.A., **117**:595-600. 1941.
381. Miller, H. E. The Occurrence of Leukopenia in Hodgkin's Disease, Lymphogranuloma. Am. J. M. Sc., **173**:490-502. 1927.
382. Miller, H. E. Lymphogranulomatosis Cutis; Hodgkin's Disease. Arch. Dermat. & Syph., **17**:156-181. 1928.
383. Miller, F. R., and Turner, D. L. Symposium on Recent Advances in Medicine; Leukemias. M. Clin. North America, **28**:1376-1385. 1944.
384. Mills, E. S., and Pritchard, J. E. Clinical and Pathological Features of a Series of 20 Cases of Hodgkin's Disease. Canad. M. A. J., **33**:50-58. 1935.

385. Minot, G. R. Megakaryocytes in Peripheral Circulation. J. Exper. Med., **36**:1-7. 1922.
386. Minot, G. R., Buckman, T. E., and Isaacs, R. Chronic Myelogenous Leukemia; Age Incidence, Duration and Benefit Derived from Irradiation. J.A.M.A., **82**:1489-1494. 1924.
387. Minot, G. R., and Isaacs, R. Lymphatic Leukemia; Age Incidence, Duration and Benefit derived from Irradiation. Boston M. & S. J., **191**:1-9. 1924.
388. Minot, G. R., and Isaacs, R. Lymphoblastoma; Aspects Concerning Abdominal Lesions, Especially their Production of Early Symptoms. Am. J. M. Sc., **172**: 157-173. 1926.
389. Minot, G. R., and Isaacs, R. Lymphoblastoma (Malignant Lymphoma); Age and Sex Incidence, Duration of Disease, and Effect of Roentgen-ray and Radium Irradiation and Surgery. J.A.M.A., **86**: 1185-1189. 1926.
390. Minot, G. R., and Spurling, R. G. The Effect on the Blood of Irradiation, Especially Short Wave Length Roentgen-ray Therapy. Am. J. M. Sc., **168**: 215-241. 1924.
391. Montgomery, A. H. Hodgkin's Disease of Bones. Ann. Surg., **87**:755-766. 1928.
392. Montgomery, H. Mycosis Fungoides, Lymphoblastoma of the Skin and Allied Conditions as General Diseases. Oxford Medicine, **4**, part 1, (44)(1)-(44)(19). 1920.
393. Mora, J. M. Granulomatous Tumor Following Intramammary Injection of Colloidal Thorium Dioxide. J.A.M.A., **115**:363-364. 1940.
394. Morrison, M., and Samwick, A. A. Clinico-Hematologic Evaluation of Bone Marrow Biopsies. Am. J. M. Sc., **198**:758-773. 1939.
395. Mottram, J. C., and Russ, S. Lymphopenia Following Exposures of Rats to "Soft" X-Rays and the B-Rays of Radium. J. Exper. Med., **34**:271-273. 1921.
396. Murray, G. R. Allbutt's System of Medicine. Hodgkin's Disease, **5**:573-596. 1897.
397. Murray, M. F. Apparent Cure of Mediastinal Hodgkin's Disease. Clin. Misc. Mary I. Bassett Hosp., **2**: 135-147. 1935.
398. Musser, J. H. Generalized Adenopathy; Diagnosis of Hematuria; Presentation of a Case of Hodgkin's Disease. Clinics, **1**:107-116. 1942.
399. Nauts, H. C., Swift, W. E., and Coley, B. L. The Treatment of Malignant Tumors by Bacterial Toxins as Developed by the late William B. Coley; Reviewed in the Light of Modern Research. Cancer Research, **6**:205-216. 1946.
400. Nettleship, A. The Lymphomatous Diseases. Bull. Alexander Blain Hosp., **5**:55-65. 1946.
401. Nichols, R. E. Study of the Phenomenon of Erythrocyte Sedimentation; Critical Survey of Literature. J. Lab. & Clin. Med., **27**:1317-1327. 1942.
402. Nitshe, G. A., and Cohen, P. P. Serum Protein Changes In Myelogenous and Lymphocytic Leukemias and Hodgkin's Disease. Blood, **2**:363-370. 1947.
403. Oakey, R. S., Jr. Review of 52 Cases of Hogdkin's Disease. Hahnemann Monthly, **79**:139-149. 1944.
404. O'Brien, F. W. End-Results in Irradiated Hodgkin's Disease. Am. J. Roentgenol., **46**:80-88. 1941.
405. Ormsby, O. S., and Finnerud, C. W. Mycosis Fungoides; a Report of a Case with Autopsy. Arch. Derm. & Syph., **27**:631-642. 1933.
406. Owen, M. Generalized Cryptococcosis Simulating Hodgkin's Disease. Texas State J. Med., **35**:767-771. 1940.
407. Pappenheim, A. Morphologische Haematologie. Folia Haemotol., **24**:1-263. 1919.
408. Parker, F., Jr., Jackson, H., Jr., Bethea, J. M., and Otis, F. Studies of Diseases of Lymphoid and Myeloid Tissues; Coexistence of Tuberculosis with Hodgkin's Disease and Other Forms of Malignant Lymphoma. Am. J. M. Sc., **184**:694-699. 1932.
409. Parker, F., Jr., Jackson, H., Jr., Fitzhugh, G., and Spies, T. D. Studies of Diseases of Lymphoid and Myeloid Tissues; IV. Skin Reactions to Human and Avian Tuberculin. J. Immunol., **22**:277-282. 1932.
410. Parsons, P. B., and Poston, M. A. Pathology of Human Brucellosis; Report of Four Cases with One Autopsy. South. M. J., **32**:7-13. 1939.
411. Parsons, P. B., Poston, M. A., and Wise, B. Pathology of Human Brucellosis. Am. J. Path., **15**:634-637. 1939.
412. Peacocke, G. Hodgkin's Disease Occurring in Twins. Dublin J. Med., Sci., **120**:85-89. 1905.
413. Peake, J. D. Leukemias, Hodgkin's Disease and Lymphosarcoma; Brief Discussion and Treatment. J.M.A. Alabama, **12**:296-300. 1943.
414. Peirce, C. B., Jacox, H. W., and Hildreth, R. C. Roentgenologic Considerations of Lymphoblastoma. Roentgen Pulmonary Pathology of the Hodgkin's Type. Am. J. Roentgenol., **36**:145-164. 1936.
415. Pepper, O. H. P. Report of a Case of Hodgkin's Disease with General Eosinophilia. Bull. Ayer Clin. Lab., Pennsylvania Hosp., **4**:22-25. 1908.
416. Pett, R. G. Irradiation of Cutaneous Manifestations of Lymphogranuloma. Pennsylvania M. J., **42**:387-391. 1939.
417. Pfahler, G. E. Mediastinal Glandular Tuberculosis in Adult Resembling Hodgkin's Disease; Recovery of Case. Am. J. Roentgenol., **41**:742-748. 1939.
418. Phillips, R. Hodgkin's Disease in the Bladder. Lancet, **240**:480. 1941.
419. Piney, A. Endotheliomas. Arch. Path., **2**:301-317. 1926.
420. Plá, J. C., Sanchez, Perez, A., and Granotich, J. P. Neurolymphogranulomatous Syndromes with Report of Cases, Arch. Clín. Méd., **2**:377–393. 1944.
421. Poston, M. A., and Parsons, P. B Isolation of Brucella from Lymph Nodes. J. Infect. Dis., **66**:86-99. 1940.
422. Potter, E. L. Hodgkin's Disease, with Special Reference to Its Differentiation from Other Diseases of Lymph Nodes. Arch. Path., **19**:139-158. 1935.
423. Priesel, A., and Winkelbauer, L. Placentare Uebertragung des Lymphogranuloms. Virchows Arch. f. path. Anat., **262**:749-765. 1926.
424. Pullinger, B. D. Histology and Histogenesis. Rose Research on Lymphadenoma. Bristol, England: John Wright and Sons, Ltd. 1932, pp. 117-136.
425. Pulvertaft, R. J. V. Treatment of Lymphadenoma with Chicken Serum. Lancet, **2**:857-858. 1933.
426. Pusch, L. C. Hodgkin's Disease of the Duodenum. Pennsylvania M. J., **45**:20-21. 1941.
427. Rabinowitch, I. M. The Diazo-color Reaction Found in Uremia. Arch. Int. Med., **45**:282-286. 1930.
428. Rae, A. S. L. Case of Hodgkin's Disease with Cutaneous and Cerebral Manifestations. Edinburgh M. J., **46**:400-405. 1939.

429. Ramos, E. Modern Ideas on Hodgkin's Disease. Prensa med. Argent., **29**:889-896. 1942.
430. Randall, E., Jr. Internal Hodgkin's Disease. Texas State J. Med., **34**:751-753. 1939.
431. Reed, D. M. On the Pathological Changes in Hodgkin's Disease with Special Reference to Its Relation to Tuberculosis. Johns Hopkins Hosp. Rep., **10**:133-196. 1902.
432. Reeves, R. J. Lymphoblastoma (Hodgkin's Disease) of the Orbit. Am. J. Roentgenol., **17**:642-645. 1927.
433. Reimann, H. A., Havens, W. P., and Herbut, P. A. Hodgkin's Disease with Specific Lesions Appearing First in the Skin. Arch. Int. Med., **70**:434-443. 1942.
434. Rhoads, C. P. Nitrogen Mustards in the Treatment of Neoplastic Disease; Official Statement. J.A.M.A., **131**:656-658. 1946.
435. Rhoads, C. P., and Abels, J. C. The Administration of Egg White and Avidin Concentrates to Patients with Cancer. J.A.M.A., **121**:1261. 1943.
436. Ribeiro, E. B. Hodgkin's Disease and Obstruction of Small Intestine. Bol. San. Sao Lucas, **5**:131-134. 1944.
437. Ritchie, H. Lymphadenoma. M. J. Australia, **1**: 197-199. 1935.
438. Ritvo, M. Hodgkin's Disease; Report of Case with Unusual Longevity and Invasion of Heart and Pericardium. New England J. Med., **223**:891-895. 1940.
439. Rolleston, H. Lymphadenoma (Hodgkin's Lymphogranuloma). Lancet, **209**:1208-1217. 1925.
440. Rosenberg, D. H., and Bloch, L. The Gordon Test For Hodgkin's Disease. J.A.M.A., **106**:1156-1158. 1936.
441. Rosenman, R. H. Spontaneous Regression of Metastatic Sarcoma. Am. J. Clin. Path., **16**:281-289. 1946.
442. Rosenthal, S. R. Significance of Tissue Lymphocytes in the Prognosis of Lymphogranulomatosis. Arch. Path., **21**:628-646. 1936.
443. Ross, J. M. The Pathology of the Reticular Tissue Illustrated by Two Cases of Reticulosis with Splenomegaly and a Case of Lymphadenoma. J. Path. & Bact., **37**:311-329. 1933.
444. Roth, G. M., and Watkins, C. H. Leukocyte Picture in Hodgkin's Disease. Proc. Staff Meet., Mayo Clin., **11**:593-597. 1936.
445. Rottino, A. Personal communication.
446. Rottino, A., and Stern, K. Electrophoretic Patterns from Serum of Patients with Hodgkin's Disease. J. Lab. & Clin. Med. In Press.
447. Rous, P. A Sarcoma of the Fowl Transmissible by an Agent Separable from the Cells. J. Exper. Med., **13**:397-411. 1911.
448. Rous, P. The Nearer Causes of Cancer. J.A.M.A., **122**:573-581. 1943.
449. Rous, P., Murphy, J. B., and Tytler, W. H. The Role of Injury in the Production of a Chicken Sarcoma by a Filterable Agent. J.A.M.A., **58**:1751. 1912.
450. Rous, P., Murphy, J. B., and Tytler, W. H. A Filterable Agent the Cause of a Second Chicken Tumor, and Osteochondrosarcoma. J.A.M.A., **59**:1793-1794. 1912.
451. Sailer, S. Hodgkin's Disease in the Aged. Am. J. Clin. Path., **6**:241-252. 1936.
452. Sanders, W. E. The Pathology and Diagnosis of Diseases of the Hemopoietic System. J. Iowa State M. Soc., **8**:423-428. 1918.
453. Sayago, C. Radium Therapy in Hodgkin's Disease. Am. J. Roentgenol., **42**:888-889. 1939.
454. Schacher, J., Browne, J. S. L., and Selye, H. Effects of Various Sterols on Thymus in the Adrenalectomized Rat. Proc. Soc. Exper. Biol. & Med., **36**:488-491. 1937.
455. Schiller, W., and Sloan, L. H. Hodgkin's Disease; Clinical and Pathological Conferences at Cook County Hospital. M. Clin. North America, **26**:283-296. 1942.
456. Schreiner, B. F. Radiation Therapy in 46 Cases of Lymphogranuloma (Hodgkin's Disease). Am. J. Roentgenol., **12**:133–137. 1924.
457. Schreiner, B. F., and Mattick, W. L. Results of Radiation Therapy in Leukemia and Lymphogranuloma. J. Cancer Research, **8**:504-514. 1924.
458. Schultz, E. G. Die Strahlenbehandlung der Lymphogranulomatose. Ergebn. d. med. Strahlenforsch., **7**: 457-512. 1936.
459. Schutt, W. Beitrag zur Lehre vom Lymphogranulom. Virchows Arch. f. path. Anat., **230**:289-291. 1921.
460. Schwind, J. L., and Hyde, G. M. Hodgkin's Disease in an Infant; Report of Case with a Peculiar Peripheral Blood Picture. J. Pediat., **21**:238-245. 1942.
461. Selye, H. Studies on Adaptation. Endocrinology, **21**:169-188. 1937.
462. Senear, F. E. Lymphoblastoma Cutis. M. Clin. North America, **26**:1-12. 1942.
463. Shapiro, P. T. Changes of Spinal Cord in Hodgkin's Disease; Report of Two Cases, with Unusual Skin Manifestation in One. Arch. Neurol. & Psychiat., **24**: 509-524. 1930.
463a. Shear, M. J., and Associates. Approaches to Tumor Chemotherapy. A. A. A. S. Washington, D. C. 1947. pp. 260–287.
464. Shelmire, B. Hodgkin's Disease of the Skin. South. M. J., **18**:511-519. 1925.
465. Sherman, D. E. Gastro-Intestinal Manifestations of Lymphogranulomatosis (Hodgkin's Disease). Arch. Int. Med., **61**:60-82. 1938.
466. Shrader, E. L., Sante, L. R., and Anderson, W. A. D. Lymphoblastoma of Hodgkin's Sarcoma Type. Radiology, **43**:293-296. 1944.
467. Silvestroni, E. Acid-Base Equilibrium in the Urine of Cancer Patients During and After Radiological or Surgical Treatment. Tumori, **11**:442-481. 1937.
468. Silvestroni, E. Acid-Base Equilibrium of Cancer Patients During and After Radiologic or Surgical Treatment. Tumori, **12**:1-46. 1937.
469. Simmons, C. C. Hodgkin's Disease, a Pathological Analysis of Nine Cases. J. Med. Research, **4**:378–400. 1903.
470. Simmons, C. C., and Benet, G. Hodgkin's Disease; a Report of Cases. Boston M. & S. J., **177**:819-834. 1917.
471. Simon, S. M. Hodgkin's Disease with Terminal Miliary Tuberculosis. M. Bull. Vet. Admin., **21**:97-98. 1944.
472. Simonds, J. P. Sarcoma and Tuberculosis; Report of a Case. Bull. Johns Hopkins Hosp., **22**:17-20. 1911.
473. Simonds, J. P. Leukemia, Pseudoleukemia and Related Conditions in Slye Stock of Mice. J. Cancer Research, **9**:329-373. 1925.
474. Simonds, J. P. Review of Hodgkin's Disease. Arch. Path., **1**:394-430. 1926.
475. Singer, H. A. Primary Isolated Lymphogranulomatosis of the Stomach. Arch. Surg., **22**:1001-1017. 1931.

476. Singher, H. O., Abels, J. C., Craver, L. F., and Rhoads, C. P. Administration of Heptylaldehyde Bisulfite to Patients with Lymphomas. Cancer Research, **4**:444-446. 1944.

477. Slaughter, D. P., and Craver, L. F. Hodgkin's Disease; 5 Year Survival Rate; Value of Early Surgical Treatment; Notes on 4 Cases of Long Duration. Am. J. Roentgenol., **47**:596-606. 1942.

478. Smeltzer, C. C. Hodgkin's Disease; Special Reference to Survival. J. Tennessee State M. A., **38**:281-286. 1945.

479. Smith, C. A. Hodgkin's Disease in Childhood; A Clinical Study with a Resume of Literature to Date. J. Pediat., **4**:12-38. 1934.

480. Smith, E. C. Hodgkin's Disease in Natives of Nigeria; Results of Biological Test. Lancet, **229**:874-877. 1935.

481. Spangler, C. C. Hodgkin's Disease of Intestine Producing Intestinal Obstruction. Am. J. Surg., **49**:121-123. 1940.

482. Spiesman, M. G., and Rubenstein, H. I. Lymphogranuloma (Rectal Stricture) Ann. Int. Med., **17**: 349-358. 1943.

483. Spurr, C. L., Jacobson, L. O., Smith, T. R., and Guzman-Barron, E. S. The Clinical Application of Methyl-Bis (B-chloroethyl) Amine Hydrochloride to the Treatment of Lymphomas and Allied Dyscrasias. Approaches to Tumor Chemotherapy. A.A.A.S., Washington, D. C. 1947, pp. 306-318.

484. Stalker, L. K., Schlotthauer, C. F., and Feldman, W. H. Probable Hodgkin's Disease in a Dog; Report of Case. Am. J. Cancer, **28**:595-602. 1936.

485. Steinberg, B., and Martin, R. A. Differentiation of Some Disorders of the Lymphatic System by Leukoagglutination. J. Immunol., **53**:137-141. 1946.

486. Steiner, P. E. Hodgkin's Disease; Search for Infective Agent and Attempts at Experimental Reproduction. Arch. Path., **17**:749-763. 1934.

487. Steiner, P. E. Etiology of Hodgkin's Disease; Skin Reactions to Avian and Human Tuberculin Proteins in Hodgkin's Disease. Arch. Int. Med., **54**:11-17. 1934.

488. Steiner, P. E. Malignant Lymphogranulomatous (Hodgkin's Disease) Cirrhosis of the Liver. Am. J. Path., **13**:109-120. 1937.

489. Steiner, P. E. Reliability and Significance of the Gordon Test in Hodgkin's Disease. Arch. Path., **31**: 1-10. 1941.

490. Steiner, P. E. Hodgkin's Disease; Incidence, Distribution, Nature and Possible Significance of Lymphogranulomatous Lesions in Bone Marrow; Review with Original Data. Arch. Path., **36**:627-637. 1943.

491. Stenhouse, H. M. Significance of Cholesterol in Tropical Hydrocele. Am. J. Trop. Med., **6**:143-151. 1926.

492. Sternberg, C. Über eine eigenartige unter dem Bilde der Pseudoleukämie verlaufende Tuberculose des lymphatischen Apparates. Ztschr. f. Heilk., **19**:21-90. 1898.

493. Sternberg, C. Lymphogranulomatose und Reticuloendotheliose. Ergebn. d. allg. Path. u. path. Anat., **30**:1-76. 1936.

494. Stevens, R. H. Radium Poisoning. Radiology, **39**: 39-47. 1942.

495. Stewart, F. W., and Doan, C. A. An Analysis of the Lymphadenopathy Question with Special Reference to Hodgkin's Disease and Tuberculosis. Ann. Surg., **93**:141-152. 1931.

496. Stewart, H. L. Etiologic Studies in Hodgkin's Disease. J. Lab. & Clin. Med., **18**:281-287. 1932.

497. Stewart, S. G. Eosinophilic Hyperleukocytosis in Hodgkin's Disease with Familial Eosinophilic Diathesis. Arch. Int. Med., **44**:772-783. 1929.

498. Stewart, M. J., and Dobson, J. F. Inoculation and Implantation Experiments in Monkeys with Glands from Cases of Hodgkin's Disease. Brit. J. Exper. Path., **5**:65-68. 1924.

499. Stone, K. Studies with the Complement Fixation Test for the Purpose of Identifying Yeasts. Rose Research on Lymphadenoma. Bristol, England: John Wright and Sons, Ltd. 1932, pp. 79-92. .

500. Sugarbaker, E. D., and Craver, L. F. Lymphosarcoma, a Study of 196 Cases with Biopsy. J.A.M.A., **117**:7-23; 112-117. 1940.

501. Sung, J. K. S., Taylor, H. B., and Roots, L. H. Hodgkin's Disease in North Anhwei; Report of Case. Chinese M. J., **52**:279-280. 1937.

502. Sweitzer, S. E., and Winer, L. H. Ulcerative Hodgkin's Disease and Lymph Node Imprints. Arch. Dermat. & Syph., **51**:229-236. 1945.

503. Symmers, D. Clinical Significance of Pathological Changes in Hodgkin's Disease. Am. J. M. Sc., **167**: 155-177; 313-339. 1924.

504. Symmers, D. Clinical Significance of the Deeper Anatomic Changes in Lymphoid Disease. Arch. Int. Med., **74**:163-171. 1944.

505. Symmers, D. Giant Cells in Hodgkin's Disease; Ancient Error in Modern Medicine. J.A.M.A., **128**: 1248-1249. 1945.

506. Terplan, K., and Mittelbach, M. Beiträge zur Lymphogranulomatose und zu anderen eigenartigen, verallgemeinerten Granulomen der Lymphknoten. Virchow's Arch. f. path. Anat. **271**:759-866. 1929.

507. Thomas, T. B., Ewing, P. L., and Emerson, G. A. The Effect of a Bone-Marrow-Spleen Immune Serum in Cytology of the Spleen; Potentialities as a Bioassay Method. Fed. Proc., **5**:207. 1946.

508. Torrey, J. C. Bacteria Associated with Certain Types of Abnormal Lymph Glands. J. Med. Research, **29**:65-80. 1916.

509. Townsend, S. R., and Braunstein, A. L. Hyperchromic Macrocytic Anaemia in Association with Hodgkin's Disease. Canad. M. A. J., **41**:254-257. 1939.

510. Tulloch, W. J. Notes on the Reaction of Tissues to Infection with Virus Agent. International Congress Microbiol. Rep. II. 1936. p. 110.

511. Turner, J. C., Jackson, H., Jr., and Parker, F. Jr. Etiologic Relation of Eosinophils to Gordon Phenomenon in Hodgkin's Disease. Am. J. M. Sc., **195**:27-32. 1938.

512. Twort, C. C., and Archer, H. E. Experimental Production of a Fatal Nephritis with Filter-passing Virus of Nervous Origin. Lancet, **204**:1102-1106. 1923.

513. Twort, C. C. The Relation of the Tubercle Bacillus to Lymphadenoma. J. Hyg., **23**:260-267. 1924.

514. Twort, C. C. Etiology of Lymphadenoma; Summary of 6 Years Researches. J. Path. & Bact., **33**: 539-546. 1930.

515. Twort, C. C., Todd, E. W., and Perkins, R. J. Group Specificity of Some Antigens Derived from Acid-Fast Bacilli. Brit. J. Exper. Path., **5**:171-174. 1924.

516. Tyslowitz, R., and Dingemanse, E. Effect of Large Doses of Estrogen on the Blood Picture of Dogs. Endocrinology, **29**:817-827. 1941.

517. Tyzzer, E. E. Tumor Immunity. J. Cancer Research, **1**:125-153. 1916.

518. Uddstromer, M. On the Occurrence of Lymphogranulomatosis in Sweden 1915-1931 and Some Considerations as to Its Relation to Tuberculosis. Copenhagen: Levin and Munksgaard. Acta Tuberculosa Scand., Supplement No. 1, 1-225. 1934.

519. Utz, L., and Keatinge, L. Hodgkin's Disease; A Treatise. M. J. Australia, **1**:521-537. 1932.

520. van Rooyen, C. E. Etiology of Hodgkin's Disease with Special Reference to B. Tuberculosis Avis. Brit. M. J., **1**:50-51. 1933.

521. van Rooyen, C. E. Recent Experimental Work on the Aetiology of Hodgkin's Disease. Brit. M. J., **2**: 562-563. 1933; 519-524. 1934.

522. van Rooyen, C. E. Some Properties of the Encephalitogenic Agent in Lymphadenomatous Tissue. Brit. M. J., **1**:519-524. 1934.

523. van Rooyen, C. E. Interpretation and Significance of Gordon's Test in Hodgkin's Disease; Study of 100 Cases. Edinburgh M. J., **44**:455-464. 1937.

524. Vasiliu, T. La Lymphogranulomatose (Maladie de Paltauf-Sternberg). Ann. d'Anat. Path., **8**:815-837. 1931.

525. Vasiliu, T., and Goia, I. La Granulomatose Maligne. Ann. d'Anat. Path., **4**:33-62. 1927.

526. Versé, M. Die Lymphogranulomatose der Lunge und der Brustfells. In Handbuch der Speziellen Pathologischen Anatomie und Histologie. Edited by Henke and Lubarsch. Part 3. Berlin: Julius Springer. 1931, pp. 280-343.

527. Vianna, J. B. Hodgkin's Disease. Hora med. Rio de Janiero, **1**:9-11. 1943.

528. Vieta, J. O., Friedell, H. L., and Craver, L. F. A Survey of Hodgkin's Disease and Lymphosarcoma in Bone. Radiology, **39**:1-15. 1942.

529. Virchow, R. Weisses Blut. Neue Notizen aus dem Gebiet der Natur-und Heilkunde (Froriep's Neue Notizen), **36**:161. 1845.

530. Vogt, A. Utilization of Vitamin C in Tumor Patients and in Lymphogranulomatosis.. Strahlentherapie, **65**: 616–623. 1939. Chem. Abstr. **33**:9417. 1939.

531. von Braitenberg, H. Congenital Lymphogranulomatosis. Beitr. zur. Anat. u. z. Allg. Path., **101**:301. 1938.

532. Voyles, G. Q., and Beck, E. M. Systemic Infection Due to Torula Histolytica; Report of 4 Cases and Review of Literature. Arch. Int. Med., **77**:504-515. 1946.

533. Voyles, G. Q., and Beck, E. M. Systemic Infection Due to Torula Histolytica; Effect of Chemotherapeutic Agents in Experimentally Produced Infections. Arch. Int. Med., **77**:516-525. 1946.

534. Wachsmuth, W. On the Grafting of Lymph Nodes from Cases of Lymphogranuloma. Deutsche Ztschr. f. Chir., **208**:41-45. 1928.

535. Waetzoldt. Pseudoleukemie oder chronische Miliartuberkulose. Centralbl. f. klin. Med., **11**:809-815. 1890.

536. Waldman, S. Hodgkin's Disease in the Aged Associated with Diabetes Mellitus. Med. Rec., **152**:292. 1940.

537. Wallhauser, A., and Whitehead, J. M. Immunological Method in Hodgkin's Disease. Am. J. Surg., **5**:229-233. 1928.

538. Wallhauser, A. Hodgkin's Disease. Arch. Path., **16**: 522-562; 672-712. 1933.

539. Warrington. Two Clinical Studies of the Enlargement of the Spleen. Liverpool Medico-Chir. J., **28**: 74. 1908.

540. Warfield, L. M., and Kristjanson, H. T. An Unusual Case of So-Called Pseudoleukemia (Lymphosarcoma). Am. J. M. Sc., **152**:222-230. 1916.

541. Warner, E. C. Discussion of the Aetiology and Diagnosis of Lymphadenoma. Proc. Roy. Soc. Med., **30**: Section 1, 543-549. 1930.

542. Warner, E. C. Treatment of Lymphadenoma with Sensitized Vaccine of Elementary Bodies. Lancet, **231**:417-421. 1936.

543. Warthin, A. S. Genetic Neoplastic Relationships of Hodgkin's Disease, Aleukemic and Leukemic Lymphoblastoma, and Mycosis Fungoides. Ann. Surg., **93**: 153-161. 1931.

544. Warthin, A. S., and Weller, C. V. The Medical Aspects of Mustard Gas Poisoning. St. Louis: C. V. Mosby. 1919.

545. Watson, G. F. Spleen Therapy in Tuberculosis. Canad. M. J., **22**:31-33. 1930.

546. Watson, G. F., Diller, I. C., and Ludwick, N. V. Spleen Extract and Tumor Growth. Science, **106**: 348. 1947.

547. Webster, J. H. D. The Periodicity and Cause of Cancer, Leukemia, and Allied Tumors. Wood: Bailliere, Tindall and Cox. 1940.

548. Weil, A. Spinal Cord Changes in Lymphogranulomatosis. Arch. Neurol. & Psychiat., **26**:1009-1026. 1931.

549. White, P. A., and Senty, E. G. Hodgkin's Disease; Report of Cases Including One with Pruritus and Pel-Ebstein Type of Relapsing Fever. J Iowa M. Soc., **23**:70-74. 1933.

550. Wile, U. J., and Stiles, F., Jr. Clinical Mutations in Lymphoblastomas. J.A.M.A., **104**:532-537. 1935.

551. Wilks, S. Cases of Lardaceous Disease and Some Allied Affections. Class V-Cases of a Peculiar Enlargement of the Lymphatic Glands Frequently Associated with Disease of the Spleen. Guy's Hosp. Rep., **2**:103-132. 1856.

552. Wilks, S. Cases of Enlargement of the Lymphatic Glands and Spleen. Guy's Hosp. Rep., **11**:56-67. 1865.

553. Williams, W. L. The Effects of Suramin (Germanin), Azo Dyes and Vasodilators on Mice with Transplanted Lymphosarcomes. Cancer Research, **6**: 344-354. 1946.

554. Williams, W. S., and Neuburger, K. T. A Case of Hodgkin's Disease with Marked Eosinophilia. Rocky Mt. M. J., **41**:320-322. 1944.

555. Winkelman, N. W., and Moore, M. T. Lymphogranulomatosis (Hodkin's Disease) of Nervous System. Arch. Neurol. & Psychiat. **45**:304-318. 1941.

556. Wintrobe, M. M., McLennan, M. T., and Huquley, C. M. Clinical Experiences with Nitrogen Mustard Therapy. In Approaches to Tumor Chemotherapy. A.A.A.S. Washington, D. C. p.347-357. 1947.
557. Wise, B. Sedimentation Rate in Hodgkin's Disease. J. Lab. & Clin. Med., **27**:1200-1206. 1942.
558. Wise, N. B., and Poston, M. A. Coexistence of Brucella Infection and Hodgkin's Disease; Clinical, Bacteriologic and Immunologic Study. J.A.M.A., **115**: 1976-1984. 1940.
559. Wiseman, B. K. The Blood Picture in Primary Diseases of the Lymphatic System. J.A.M.A., **107**: 2016-2022. 1936.
560. Wolpaw, S. E., Higley, C. S., and Hauser, H. Intrathoracic Hodgkin's Disease. Am. J. Roentgenol., **52**:374-387. 1944.
561. Wright, C. B. Hodgkin's Disease; 60 Cases in Which There Were Intrathoracic Lesions. J.A.M.A., **111**: 1286-1290. 1938.
562. Wurm, K. Über den Gordon Test bei Lymphogranulomatose und seine praktische Bedeutung. Deutsches Arch. f. klin. Med., **181**:90-123. 1937.
563. Yamasaki, M. Zur Kenntnis der Hodgkinschen Krankheit und ihres Uberganges in Sarkom. Ztschr. f. Heilk., **25**:269-313. 1904.
564. Yates, J. L. A Clinical Consideration of Hodgkin's Disease. Bull. Johns Hopkins Hosp., **25**:180-184. 1914.
565. Yates, J. L. Proper Treatment of Chronic Malign Diseases of the Superficial Lymph Glands. Arch. Surg., **5**:65-109. 1922.
566. Yates, J. L., and Bunting, C. H. The Rational Treatment of Hodgkin's Disease. J.A.M.A., **64**: 1953-1961. 1915.
567. Yates, J. L., and Bunting, C. H. Results of Treatment in Hodgkin's Disease. J.A.M.A., **68**:747-751. 1917.
568. Yates, J. L., Bunting, C. K., and Kristjanson, H. T. The Etiology of Splenic Anemia in Banti's Disease. J.A.M.A., **63**:2225. 1914.
569. Young, G. A., Young, R. H., and Gysin, W. M. Malignant Lymphoma with Meningeal and Polyradicular Infiltration. Nebraska M. J., **30**:434-436. 1945.
570. Zanes, R. P., Jr., and Hoster, H. A. Personal communication.
571. Ziegler, K. Die Hodgkinsche Krankheit. Jena: G. Fischer. 1911.
572. First Case of Histoplasmosis in Turkey. J.A.M.A., **131**:1239. 1946. Abstracted by Correspondent of Journal.

Changes in the Heat Coagulation of Plasma from Cancer Patients*†

Maurice M. Black, M.D., Israel S. Kleiner, Ph.D. and Herman Bolker, M.D.

(From the Brooklyn Cancer Institute, Brooklyn 9, N.Y., and the Department of Biochemistry, New York Medical College, New York 29, N.Y.)

(Received for publication June 29, 1948)

The changes in plasma protein associated with the presence of malignant neoplastic disease have been reviewed recently by Toennies (8). In a discussion of the literature several studies are quoted indicating that an increase in plasma fibrinogen occurs in a significant number of cancer cases. Although such changes are not limited to cancer they are another indication of the systemic alterations in body substrate associated with malignancy. While these alterations represent quantitative changes, it is also known that certain qualitative differences may be found. Thus Savignac, Grant and Sizer (7) reported a decrease in the reducing power of plasma from cancer patients. They believe such changes to be related to alterations in the albumin molecule. Corroboration and extension of these studies were made by Black (1, 2). In the course of these studies it was noted that plasma from cancer patients tended to undergo heat coagulation more rapidly than plasma from normal individuals. This paper is a report of the findings obtained in a study of the heat coagulation of plasma in malignant neoplastic disease, and of its diagnostic and prognostic significance.

MATERIAL AND METHODS

One cc of plasma (fasting specimen) is placed in a Klett colorimeter tube and then diluted to the 5 cc mark with distilled water. A reading of the light transmission is taken in the Klett photoelectric colorimeter using a green filter (No. 54). Immersion in a vigorously boiling water bath for just 10 seconds follows. It is important that the tube be immersed at least as far as the 10 cc mark and that sufficient water be used so that boiling is uninterrupted by the introduction of the tube. The tube is then cooled under the tap, dried, and the light transmission again determined. The difference between the first and second reading is taken as the measure of the heat coagulation or turbidity. This value will be referred to below as the coagulation reading or value. In addition the plasma samples were studied for their reducing power using the dyes methylene blue and brilliant cresyl blue according to the method of Black (3).

As many plasma samples undergo a fall in their coagulation values on standing in the refrigerator for several days, it is desirable that the determination be carried out the day the sample is drawn. This phenomenon is under investigation at present.

RESULTS

The values obtained by this procedure may be described according to the various types of patients tested; *i.e.*, those with cancer,[1] non-neoplastic diseases, and nonmalignant neoplasia; and controls (presumably healthy persons).

Controls.—Plasma samples from 434 normal persons were tested. A bell-shaped distribution curve of coagulation readings was obtained with the peak at a coagulation value of 47. As seen in Fig. 1, less than 2 per cent reached a value of 85. In general, values obtained are quite reproducible. Triplicate determinations should not differ by more than 8.

Cancer group.—In a series of 199 cases the coagulation values obtained had a much wider distribution than the control group and approximately 60 per cent were 80 or above. In view of the small percentage of controls with coagulation values above 79 it was arbitrarily decided to adopt the coagulation value of 80 or above as suggestive of the presence of malignant neoplasia. The results of the various determinations are listed in Table I.

It will be noted that there is a decided difference in these coagulation values from the results of the control group. The mean of these values was 99.

The findings in cases of sarcoma, lymphosarcoma and leukemia deserve comment. In this group only 3 out of 23 cases (13 per cent) were identified by coagulation values of 80 or more, whereas studies

* This work was aided by grants from the Leukemia Research Foundation, Inc., and the Biochemical Research Fund, New York Medical College.

† Preliminary report of this study made at the Thirty-Ninth Annual Meeting of the American Association for Cancer Research, Inc., Atlantic City, New Jersey, 1948.

[1] The word *cancer* is here used to signify all types of malignant neoplasia, sarcoma as well as carcinoma.

in the reducing power of plasma (1) identified 13 of the 20 cases, or 65 per cent. In sharp contrast to the low 13 per cent percentage for other types of malignant neoplasia, just mentioned, is the 66 per cent (115 of 176 instances) in the case of carcinoma.

It should be emphasized that the coagulation values obtained will vary somewhat when different colorimeters are used. Therefore, it is advisable for each laboratory to establish the normal limits for their own machine. When this is done the values obtained with the plasma of cancer patients will show the same type of variation reported here.

Combining the results of the dye-reducing test and the coagulation studies, cancer was considered to be present when a positive reaction was obtained with either or both tests. By the use of these criteria, cancer was identified in approximately 87 per cent of the cases tested, as shown by the data given in the last column of Table I.

The distribution of the coagulation values and the reduction times for methylene blue (2) are shown in Fig. 2.

The incidence of the various methylene blue reducing times (MBT) are indicated within each coagulation value group. As reported in the papers already referred to, a methylene blue reducing time of 11 minutes or more is considered to be suggestive of the presence of malignancy; while values of 8.5 minutes or less are considered normal. When values between 9.0 minutes and 10.5 minutes are obtained, the plasma is also tested with brilliant cresyl blue. Incomplete reduction of this dye is interpreted as suggestive of cancer, whereas complete reduction is considered to indicate a normal type of reaction. It is for this reason that these three divisions of the methylene blue values are

TABLE I: CANCER

Diagnosis	No. of cases	No. above 79	Mean	Ratio identified by combined method*
Bladder	5	5	115	5/5
Breast	36	21	90	27/33
Carcinomatosis, origin unknown	4	1	91	3/4
Cervix	12	9	120	12/12
Colon	13	9	111	13/13
Esophagus	4	4	105	4/4
Fundus uteri	11	7	95	9/10
Gall bladder	1	1	265	1/1
Hodgkins disease	12	8	104	10/12
Larynx	5	4	106	5/5
Leukemia, acute and chronic	7	0	57	5/7
Liver	2	1	58	2/2
Lung	15	12	121	13/15
Lip	2	2	105	2/2
Lymphosarcoma	8	2	83	4/8
Melanoma	3	2	131	2/2
Mouth	11	6	100	9/10
Myeloma	1	1	134	1/1
Prostate	3	1	81	3/3
Rectum	8	5	103	9/9
Sarcoma	8	1	55	6/8
Skin, basal	3	1	74	2/3
Skin, squamous	5	2	91	3/5
Stomach	9	4	81	8/9
Tongue	4	2	75	2/4
Tonsil	4	4	114	4/4
Vulva	3	3	109	3/3
Total	199	118	99	167/194

NOTE: The apparent discrepancy between some of the figures in columns 1 and column 4 is due to the fact that not all cases were tested by both methods.

* Cases identified by either or both the reducing power studies and the coagulation value.

TABLE II: NON-NEOPLASTIC DISEASES

Diagnosis	No. of cases	No. below 80	Mean	Ratio correct by combined method*
Abscess and inflammation	4	4	41	4/4
Appendicitis	1	1	28	1/1
Arthritis, rheumatoid, active	3	2	62	2/3
Asthma, bronchial	1	1	57	1/1
Breast, cyctic disease	2	2	56	2/2
Bronchiectasis	4	3	82	3/4
Cardiac failure	4	4	49	4/4
Cervicitis	2	2	55	2/2
Cholecystitis and lithiasis	4	4	60	4/4
Cirrhosis, hepatic	1	0	12	0/1
Colitis, ulcerative	1	1	50	1/1
Diabetes	2	2	41	2/2
Hyperthyroidism	2	1	88	1/2
Intestinal obstruction, mechanical	2	2	9	2/2
Lues	1	1	54	1/1
Lung abscess	5	5	62	4/4
Mastodynia	1	1	65	1/1
Menometrorrhagia	2	2	26	2/2
Menopausal syndrome	1	1	64	1/1
Nephrolithiasis	1	1	40	1/1
Pruritis, vaginal	1	1	34	1/1
Pyelonephritis	1	1	29	1/1
Rheumatic heart disease, active	7	5	67	4/7
Rheumatic heart disease, inactive	2	2	35	1/2
Salpingitis	1	1	63	1/1
Sarcoid, Beck	1	1	43	0/1
Scabies	1	1	32	1/1
Tuberculosis, active	11	7	74	4/11
Tuberculosis, inactive	1	1	69	1/1
Ulcer, peptic	6	5	55	5/6
Upper respiratory infection	1	1	41	1/1
Total	77	66	60	59/75

NOTE: The apparent discrepancy between some of the figures in columns 1 and column 4 is due to the fact that not all cases were tested by both methods.

* Cases having the control type of reaction with both reducing power and coagulation technic.

indicated in the graph. It should also be noted that all cases on the graph falling outside the double line are identified as cancer without recourse to

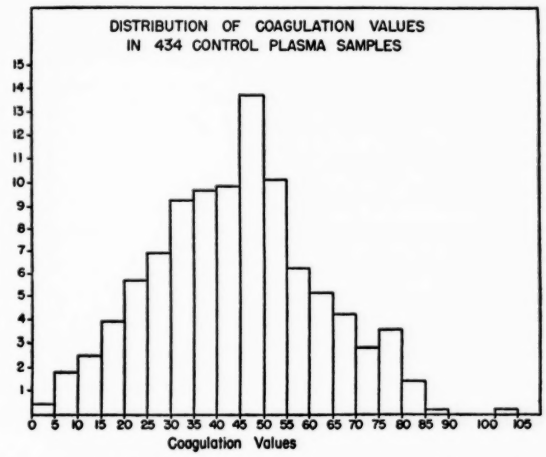


FIG. 1.—Variations in the plasma coagulation values in a series of presumably healthy persons.

testing with brilliant cresyl blue. Almost 85 per cent of the cases are thus indicated by their MBT and coagulation value.

Of 1,539 cases (Table IV) tested by the reducing time studies alone, 80 per cent of 533 cancer cases were identified. As with the coagulation studies, some cases of active tuberculosis and active rheumatic fever were indistinguishable from the malignant neoplastic group. Pregnancy, particularly in the later months, were also indistinguishable from the cancer group. Benign tumors gave reactions similar to those of the control group.

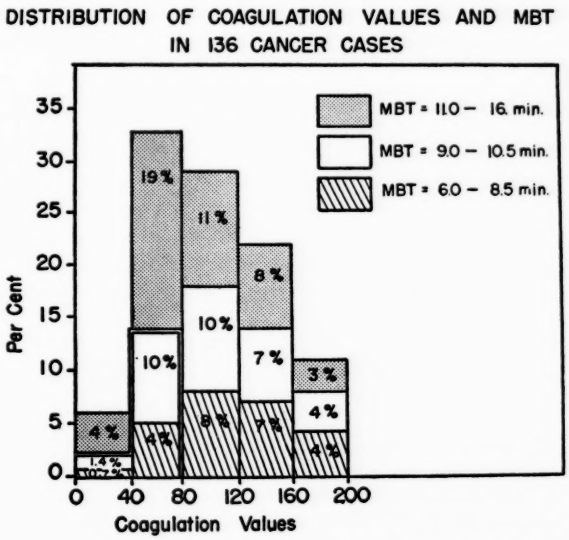


FIG. 2.—Histogram of coagulation values. The percentages in each box represent the distribution of the various (methylene blue time) values in this cancer series. Note that all cases outside the double line are identified as malignant without the use of the brilliant cresyl blue reaction.

Non-neoplastic diseases.—In this series of 78 cases, two salient facts emerge: (a) Many common diseases do not cause alterations in the coagulation values, and (b) active tuberculosis and active rheumatic heart disease do yield reactions which in some cases are indistinguishable from those in cancer patients. Results for various diseases studied thus far are listed in Table II.

As may be seen in column 4 of the table, the use of the coagulation values was somewhat more accurate here than in the reducing time studies.

The occurrence of plasma reducing power and coagulation values, which are indistinguishable from those in malignant neoplasia, indicate that the specificity of these studies is not absolute, a fact of extreme importance in the application of these findings to clinical problems.

Nonmalignant neoplasia.—The preliminary findings given in Table III appear to be more similar to the controls than to the cancer group.

DISCUSSION

It should be mentioned that an increased coagulation reaction in cancer patients is not necessarily associated with cachexia or debilitation, such as occurs more often in active tuberculosis and rheumatic fever. Table I shows that elevated coagulation reactions are encountered in cases of local skin carcinoma, also.

An effort was made to determine the factors on which the coagulation reaction depends. It was soon evident that the fibrinogen level was of some importance, for similar treatment of serum failed to show any increase in turbidity; in fact, readings were often a few points lower after exposure to heat.

Parallel chemical determinations of fibrinogen, according to the method listed by Reiner (6), revealed that an increase in the coagulation value was associated with increase in fibrinogen although no absolute stoichiometric relation existed. Thus, varied coagulation values were obtained where identical plasma fibrinogen levels existed (Fig. 3). Apparently, factors, as yet undetermined, other than fibrinogen concentration, are also involved. In view of the report by Jeener (5) that the transformation of fibrinogen to fibrin is accompanied by the oxidation of thiols to disulphides the coagulation values at various plasma fibrinogen levels were compared to the parallel reducing power studies. Since the methylene blue reducing time has been shown to be dependent on the –SH reactivity of the albumin molecule (2) it was felt that if this was a component factor in the coagulation value some correlation should be found in the cases studied. However, we

found no correlation between the reducing time and the coagulation values in cases having the same plasma fibrinogen content.

The fluctuation in the coagulation reactions in cancer patients undergoing treatment is particularly interesting from the prognostic standpoint since it provides an objective means of following the effects of a therapeutic procedure. These variations were well illustrated in a case of Hodgkin's disease that underwent several remissions and exacerbations. Fluctuations from values of 155 to 45 occurred as the patient went from an active state to one of clinical remission. With recurrence of activity the coagulation value rose to 172, only to fall to 55 as another remission was induced. Remissions in this case were induced by chemotherapeutic agents previously described by the authors (3). Similar results were also obtained in carcinoma cases after surgical resection of the lesions.

TABLE III: BENIGN TUMORS

Diagnosis	No. of cases	No. above 79	Mean	Ratio corrected by combined method*
Carotid tumor	1	0	60	1/1
Hemangioma	1	–	44	1/1
Leiomyoma uteri	6	2	64	4/6
Lipoma	2	0	44	2/2
Papilloma, skin	1	0	35	1/1
Prostatic Hypertrophy, benign	1	0	79	1/1
Thyroid adenoma	2	0	53	2/2
Xanthoma	1	0	78	1/1
Total	15	2	50	13/15

* Cases having the control type of reaction with both reducing power and coagulation technic.

SUMMARY

Plasma samples from cancer patients did not always give malignant type reactions with both the coagulation and reducing power studies, but in most cases either one or the other would be positive. Thus a malignant type of reaction was obtained in approximately 90 per cent of the cancer cases in this series with either the coagulation values or the reducing time studies. Such a high degree of accuracy in the identification of plasma samples from cancer patients warrants further study of these tests of their value as a screening method for cancer. It should be emphasized however, that similar reactions have been obtained in diseases other than malignant neoplasia (tuberculosis and rheumatic fever), and that approximately 10 per cent of the cancer patients tested were not identified by these methods. It is therefore important that these data should not be used indiscriminately. It is only with due regard for its limitations that it may be applied as an aid in the diagnosis and follow-up of cancer cases.

TABLE IV: DIAGNOSTIC ACCURACY BY COMPARISON WITH STUDIES ON REDUCING POWER

Group	Total No. of cases	No. false	Accuracy, %
Control	600	0	100
Non-Neoplastic Diseases	361	30	92
Non-Malignant Neoplasia	45	3	93
Malignant Neoplasia	533	108	80
Total	1,539	141	91

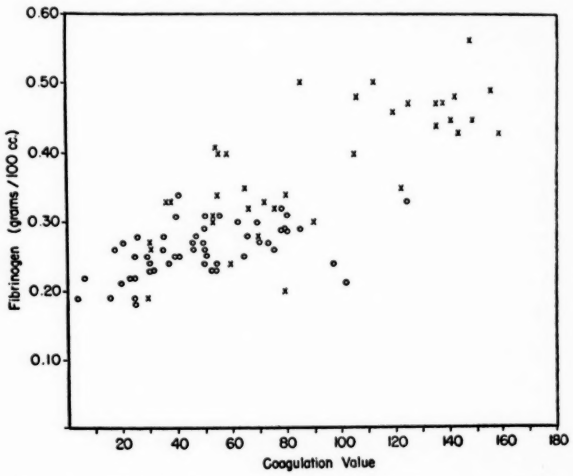


FIG. 3.—Distribution of coagulation values in relation to plasma fibrinogen content. X=Cancer Cases; O=Controls and Non-neoplastic diseases.

ACKNOWLEDGMENT

We are indebted to Dr. B. G. Kerr, Department of Surgery, Kings County and Caledonia Hospitals, for his assistance and pertinent criticism.

REFERENCES

1. BLACK, M. M. Changes in the Reducing Power of Serum or Plasma of Patients with Malignant Neoplastic Disease. Cancer Research, **7**:321–325. 1947.
2. BLACK, M. M. Sulfhydryl Reduction of Methylene Blue with Reference to Alterations in Malignant Neoplastic Disease. Cancer Research, **7**:592–594. 1947.
3. BLACK, M. M., KLEINER, I. S., and BOLKER, H. Energy Mechanisms in Malignant Tumors in Relation to Chemotherapy. Cancer Research, in Press.
4. BLACK, M. M., BOLKER, H., KLEINER, I. S., and KERR, B. G. A Diagnostic Blood Test for Malignant Neoplasia. Bull. N. Y. Med. Coll., in Press.
5. JEENER, R. The Role of Thiols in Blood Plasma Coagulation. Experientia, **3**:243–244. 1947.
6. REINER, M. Manual of Clinical Chemistry. New York: Interscience Publishers, Inc., 1941, p. 37.
7. SAVIGNAC, R. J., GRANT, J. C., and SIZER, I. W. Reducing Properties of Serum from Nonmalignant Patients and from Normal Individuals. A.A.A.S. Research Conference on Cancer 1944, pp. 241–253.
8. TOENNIES, G. Protein-Chemical Aspects of Cancer. Cancer Research, **7**:198–229. 1947.

The Incidence of Benzpyrene-Induced Sarcomas in Alloxan-Diabetic Rats

W. F. Dunning, Ph.D., M. R. Curtis, Ph.D., and C. E. Friedgood,* M.D.

(From the Department of Pathology, Wayne University College of Medicine in Cooperation with the Detroit Institute of Cancer Research, Detroit 26, Michigan)

(Received for publication June 29, 1948)

Analyses of data on the cause of death in human diabetic patients suggest a negative relationship between diabetes and cancer. The reports of Lynch (10), Joslin (8), Warren (13), and more recently Robbins and Tucker (11), on the cause of death in human cases of diabetes indicate a lower frequency of carcinoma than expected. The latter observed only 8.4 per cent of deaths from cancer in a group of 307 proved diabetics, who were autopsied, while 14.7 per cent of deaths from cancer were found in a control group of 2,800 non-diabetics. Warren (13), reported deaths due to cancer in 8 per cent, Joslin (8) in 10.6 per cent and Lynch (10) in less than 3 per cent of the diabetics. The decreased percentage of deaths from cancer could not be attributed to disparity in age between the diabetic and control groups, but no other factor was implicated. The experimental results obtained by Tannenbaum (12) and others on underfed and calorie-restricted mice suggest that the faulty carbohydrate metabolism or failure of diabetics to store glycogen might be a factor in the delayed onset or prevention of cancer. Recently, Young, Kensler and Seki (14) have reported that sarcoma-bearing mice exhibit an impairment in liver glycogen storage, which is similar to the defect seen in patients with diabetes mellitus. Goldfeder (6) showed earlier that the amount of glycogen in the transplanted tumor and in the livers of tumor-bearing mice and chickens was less than that found in analogous tissues of nontumor-bearing animals.

Dunn and McLetchie (3), and Gomori and Goldner (7) have demonstrated that diabetes mellitus could be produced experimentally in the rat by intraperitoneal injection of alloxan. Duff and Starr (2) have shown that by an adjustment of the dose of the alloxan, some rats developed chronic diabetes and survived for several months. It has also been observed (9) that rats made diabetic with alloxan have low liver glycogen levels. This suggested the possibility of an experimental test of the relation of diabetes to the incidence of an experimentally produced form of malignant disease in the rat.

MATERIAL AND METHODS

Rats of 3 inbred strains were used for the experiment. Two of the strains, Fischer Line 344 and Marshall Line 520, were albino and the third A × C Line 9935, was black agouti-irish. The rats were adults 4 to 6 months of age at the start of the experiment. They were weighed and injected intraperitoneally with varying amounts of a 5 per cent aqueous solution of alloxan monohydrate (Eastman) in a single dose. Three days after the alloxan injection, the survivors were transferred to metabolism cages and blood and urine sugar determinations were made and periodically checked thereafter. The rats surviving with a persistant glycosuria and hyperglycemia for 5 to 7 days were considered sufficiently good risks as chronic diabetics to inject subcutaneously on each side with 0.2 cc. of a 1 per cent solution of benzpyrene[1] in

TABLE I: THE NUMBER OF ACUTE AND CHRONIC DIABETIC AND ALLOXAN REFRACTIVE RATS IN EACH OF 3 STRAINS WHICH RESULTED FROM AN INTRAPERITONEAL INJECTION OF VARIOUS DOSES OF ALLOXAN

Dose mgm. per kilo	Strain	Sex	No. of rats	Acute	Chronic	Refractive
200	Marshall	♀	10	9	0	1
175	"	♂	26	10	8	8
175	"	♀	10	8	2	0
150	"	♂	20	0	4	16
100	"	♂	10	0	0	10
200	Fischer	♂	40	40	0	0
150	"	♂	20	20	0	0
125	"	♂	50	13	25	12
125	"	♀	40	24	12	4
200	A x C	♂	14	14	0	0
175	"	♂	14	1	4	9
175	"	♀	10	9	0	1
150	"	♀	30	16	10	4
150	"	♂	57	24	17	16

* Fellow of the American Cancer Society of Detroit (1945), now in the Department of Surgical Research, University of Pennsylvania, Philadelphia 4, Pa.

[1]Kindly supplied by Dr. E. V. Cowdry, Washington Univ., St. Louis

paraffin. The rats that showed only a trace or no sugar, following a sufficient dose of alloxan to produce acute diabetes in some rats of the same strain, were considered alloxan-refractive and were similarly injected with benzpyrene. In addition, 10 untested rats of each of 2 of the strains were injected with benzpyrene as controls.

All of the rats were inspected weekly and the time of observation of the first perceptible increase in size of each subcutaneous nodule was recorded. After the death of the animal, the tumors were described grossly, and sections of each tumor and all uninvolved paraffin nodules were preserved and examined microscopically.

RESULTS

The injection of alloxan as previously described (1, 3, 7), produced in some of the rats a selective necrosis of the beta cells of the islets of Langerhans, which resulted in a state of diabetes similar to diabetes mellitus in man. The most severe cases died in coma within 48 hours. The animals with persistent glycosuria became progressively more diabetic with severe weight loss, in spite of an enormous food and water consumption. Gomori and Goldner (7) reported the failure to produce diabetes in 5 hooded rats with a dose of alloxan equivalent to 200 mgm. per kilo of body weight, but Duff and Starr (2) succeeded in producing diabetes in 60 hooded rats with single doses of alloxan varying from 175 to 350 mgm. per kilo of body weight. With the smaller doses some of the animals survived for several months with a persistent diabetes.

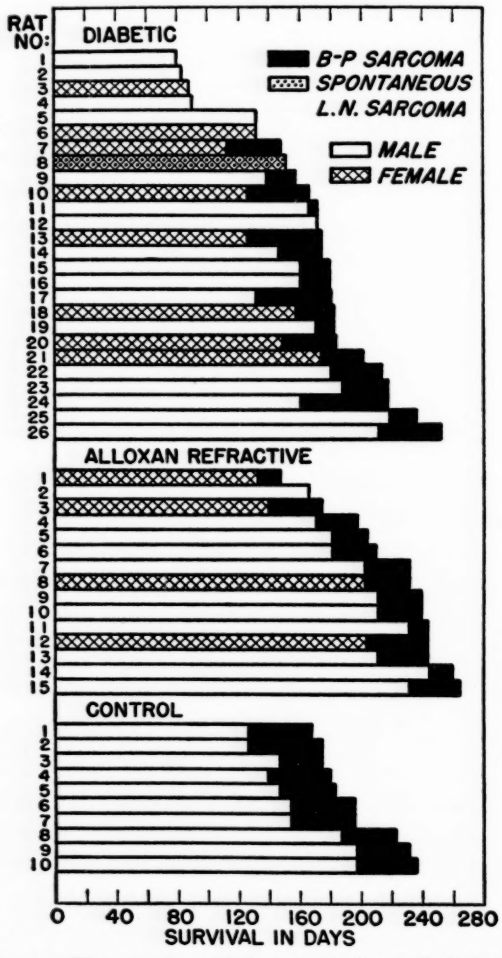


FIG. 1.—The number of days each A × C diabetic, alloxan-refractive, and control rat survived and the time of appearance of the first benzpyrene-induced sarcoma in each rat.

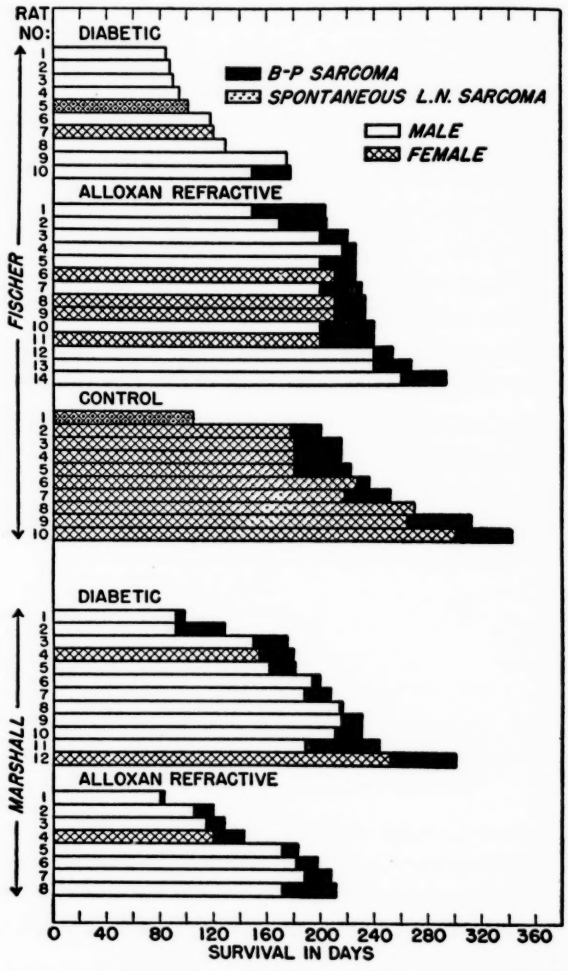


FIG. 2.—The number of days each Fischer and Marshall diabetic and alloxan-refractive rat and each Fischer control rat survived and the time of appearance of the first benzpyrene-induced sarcoma in each rat.

In the present experiment, Table I shows that all but 1 of the 64 rats which received 200 mgm. of alloxan per kilo of body weight, developed acute diabetes and died within 48 hours. The albino female of the Marshall strain that survived, appeared to be completely refractive. When the dose

was reduced to 175 mgm. per kilo, 18 of 36 Marshall rats died with acute diabetes, 10 survived as chronic diabetics and 8 were refractive. With the same dose, 10 of the 24 A × C rats developed acute fatal diabetes, 4 developed chronic diabetes and 10 were refractive. In both of the above instances, the females appeared more susceptible than the males. When the dose was further reduced to 150 mgm. per kilo of body weight, there were no acute diabetic deaths among 20 Marshall males and only 4 developed a chronic state of diabetes. All 20 Fischer males receiving this dose died within 48 hours with acute diabetes. Among the A × C rats about half of those injected with 150 mgm. per kilo died in the acute stage and nearly a third survived with a persistent diabetes. Since none of the Fischer rats survived for more than 48 hours after an injection of 150 mgm. per kilo of body weight, the dose was further reduced to 125 mgm. and this proved to be fairly effective. About 40 per cent died in the acute phase, 40 per cent developed a chronic state of diabetes and nearly 20 per cent were refractive. The females were somewhat more susceptible than the males. A dose of 100 mgm. per kilo of body weight was tried on 10 Marshall males without results. This dose might have been effective for the more susceptible Fischer female rats. Apparently the 3 strains varied considerably in their tolerance of alloxan. The most effective dose for the production of a persistent diabetes proved to be 175 mgm. per kilo of body weight for the most resistant Marshall rats, 150 mgm. for the A × C rats and 125 mgm. for the most susceptible Fischer rats.

The summary of the results obtained from the injection of benzpyrene in these three groups of rats is given in Table II and the individual cases are shown graphically in Figs. 1 and 2. The first tumor was observed 80 days after the injection of benzpyrene in a Marshall alloxan-refractive male. This was only a little longer than the minimum of 76 days previously reported (4) for a much larger series of rats similarly injected with 1 per cent benzpyrene in paraffin.

Of the 82 chronic diabetics which were injected, only 48 survived for 80 days and the average survival period for these was only 150 days. Among these 31, or 67 per cent, developed at least 1 sarcoma and 16, or 51 per cent, developed bilateral sarcomas at the sites of injection. The survival period of the diabetic rats varied considerably in the 3 strains, probably reflecting the severity of the disease. The Fischer diabetics averaged only 118 days, the A × C's 148 days and the Marshall's 178 days. The Fischer diabetics sustained a 30 per cent loss in body weight, while the A × C and Marshall diabetics lost 15 and 10 per cent, respectively. Only 1 Fischer male of the 10 surviving for 80 days developed a sarcoma, while 18 of 26 of the A × C diabetic animals developed sarcomas in one or both of the foci of injection.

All but one of the injected alloxan-refractive rats, on the other hand, survived for 80 days and 36, or 97 per cent, developed sarcoma and 17, or 47 per cent, developed tumors at both of the injection sites. Of the untested control rats all surviving the minimum latent period, 18, or 90 per cent, developed tumors at 1 or both injection sites, and 12, or 66 per cent, had bilateral sarcomas.

The statistical evaluation of the difference of 32.7

TABLE II: THE NUMBER OF RATS OF EACH GROUP WHICH WERE INJECTED WITH 3-4 BENZPYRENE, THE NUMBER AND PER CENT WHICH DEVELOPED SARCOMAS, AND THE MINIMUM AND AVERAGE LATENT PERIOD IN DAYS

Strain	Group	No. of rats injected	No. over 80 days	Aver. days to death	No. of rats with tumor	Rats with tumor, %	No. of tumors	Minimum latent period	Aver. latent period ± P.E.
Fischer	Diabetic Alloxan	37	10	118	1	10	1	149	149 ±
"	Refractive	14	14	236	14	100	22	149	208 ± 4.9
"	Control	10	10	238	8	80	11	178	217 ± 10.3
Marshall	Diabetic	14	12	178	12	100	15	91	174 ± 9.0
"	Alloxan Refractive	9	8	150	8	100	11	80	141 ± 9.2
A x C	Diabetic	31	26	148	18	69	31	113	160 ± 4.4
"	Alloxan Ref active	15	15	220	14	93	20	133	197 ± 5.7
"	Control	10	10	196	10	100	19	126	157 ± 1.7
Total	Diabetic Alloxan	82	48	150	31	67	47	91	165 ± 4.4
"	Refractive	38	37	210	36	97	53	80	189 ± 4.6
"	Control	20	20	217	18	90	30	126	184 ± 7.2

in per cent of tumor-bearing rats between the diabetic and alloxan refractive rats, which survived the minimum latent period, indicates that this difference is 5.4 times the probable error of the difference and undoubtedly significant. The fact that the most susceptible Fischer rats and probably the most severely diabetic ones had the lowest incidence of tumors and the most resistant Marshall diabetics had the highest incidence of tumors, would strengthen the argument that the inability to metabolize and store glycogen or the resultant state of inanition was a factor in the prevention of this particular form of malignant disease. A further glance, however, at the individual records in Figs. 1 and 2 show that only 5 rats which survived as long as 150 days after the injection of benzpyrene died without tumors. Three of these were diabetics, a male and a female A × C and a Fischer male rat, one was an A × C alloxan refractive rat and the other was an untested Fischer control female. All of the others that died without tumors succumbed soon after reaching the minimum latent period where the frequency of the tumor development was low.

Another measure of the relative susceptibility to experimentally induced malignant disease is the length of the latent period. It has already been noted that the shortest observed period from the injection of benzpyrene to the observation of a tumor was 80 days in an alloxan refractive rat. The minimum latent period for the diabetic rats was 91 days and for the controls, 126 days. From Table II, it appears that the only tumor in a diabetic Fischer rat was observed 149 days after the injection of benzpyrene and this was the same as the minimum latent period observed for Fischer alloxan refractive rats. The average latent periods of Fischer alloxan refractive and control rats were approximately equal, or 208± 4.9 and 217± 10.3 days, respectively. For the Marshall rats the average latent period was longer for the diabetic rats (174± 9.0 days) than for the alloxan-refractive Marshall rats (141± 9.2 days), but the difference was not significant. For the A × C rats the average latent period was approximately the same for the diabetic and control rats (160± 4.4 and 157± 1.7 days, respectively), but was significantly longer (197± 5.7 days) for the alloxan-refractive rats.

Considering the group as a whole, the benzpyrene-induced tumors appeared in diabetic rats in an average of 165± 4.4 days, in alloxan-refractive rats in 189± 4.6 days and in the control rats 184± 7.2 days. The average latent period was significantly longer in the alloxan-refractive than in the diabetic rats, indicating a greater rather than a reduced susceptibility among the latter. However, the average latent period observed for these diabetic rats was very close to the average previously observed (164± 2.3 days) for a series of 229 tumors induced in normal rats with the same dose of benzpyrene (5), and the average latent periods for the control and alloxan refractive rats both fall within the limit of this mean, plus its standard deviation (52.4± 1.6 days).

The evidence from this experiment, therefore, shows that the diabetic condition induced by alloxan shortened the life span of the affected animals, thereby reducing both the percentage that lived long enough to develop sarcoma and the average latent period in those which did, but did not prevent or delay the onset of the experimentally induced malignant process in rats surviving the average time of occurrence of these tumors.

The morphology of the tumors varied somewhat, but the majority, or 115, were classified as fibrosarcomas. Figs. 3 and 4 are fairly representative of the variation observed in the degree of cellularity. The more unusual types included 6 rhabdomyosarcomas (Fig. 5), 3 liposarcomas (Fig. 6) and 2 osteosarcomas. The tumors in the diabetic rats included 42 fibrosarcomas, 1 liposarcoma and 4 which were unclassified. Among the alloxan-refractive rats 44 fibrosarcomas, 5 rhabdomyosarcomas, 2 liposarcomas, and 2 osteosarcomas were observed. The tumors in the control rats included 29 fibrosarcomas and 1 rhabdomyosarcoma. Also, the rarer types of tumor appeared to be distributed at random among the rats of the 3 strains, the rhabdomyosarcoma occurring in 3 Fischer and 3 A × C rats, the liposarcoma in 1 A × C and 2 Marshall rats and the osteosarcoma in 1 Fischer and 1 Marshall rat.

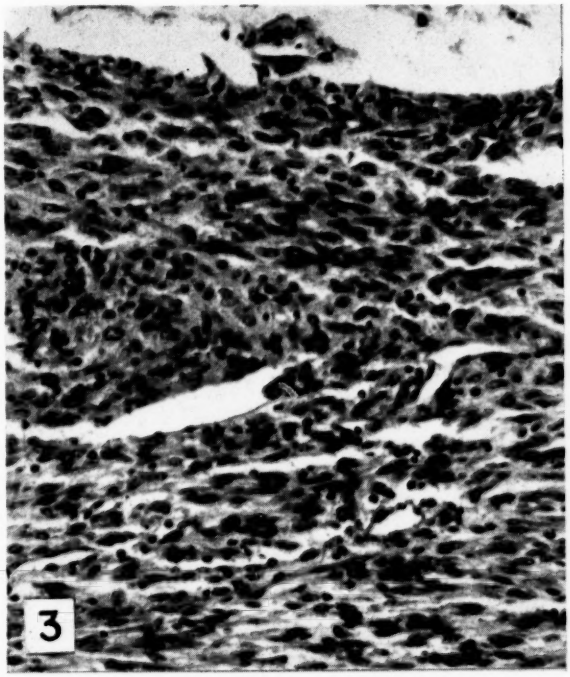
SUMMARY

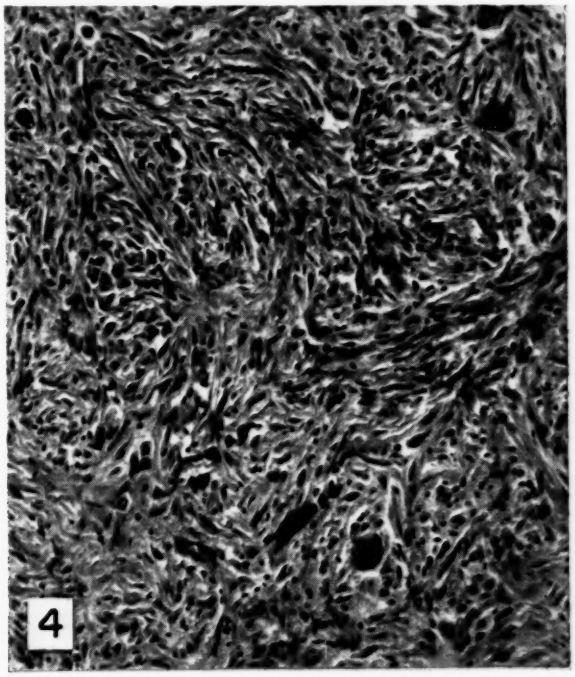
1. A 5 per cent aqueous solution of alloxan monohydrate was injected intraperitoneally in 351 rats of 3 distinct inbred strains in doses varying from 100 to 200 mgm. per kilo of body weight.

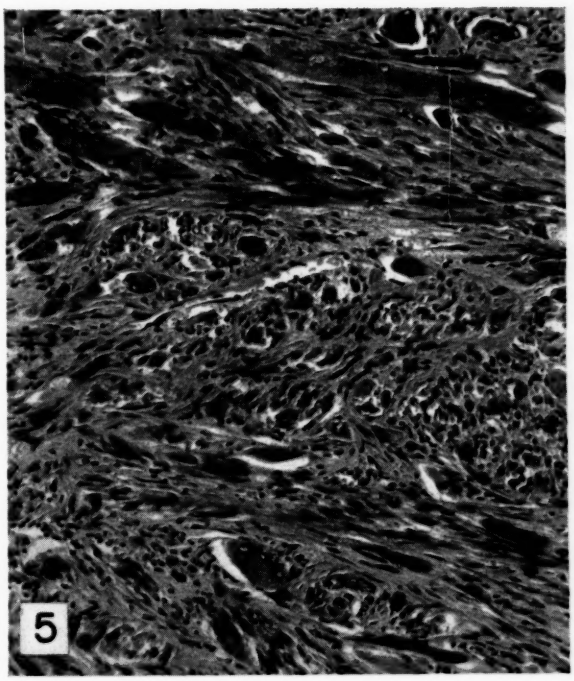
2. Within 48 hours after the injection, 188, or 54 per cent, of these rats died in diabetic coma, 82, or 23 per cent, survived with a persistent glycosuria and 81, or 23 per cent, were refractive to the alloxan.

3. The rats of the 3 strains varied in their tolerance to alloxan, the optimum dose for producing a chronic state of diabetes varying from 125 mgm. per kilo of body weight for rats of the most susceptible strain to 175 mgm. for the rats of the most resistant strain.

4. The 82 chronic diabetics, 38 of the alloxan-refractive, and 20 untested control rats of the 3 strains were injected subcutaneously in both sides







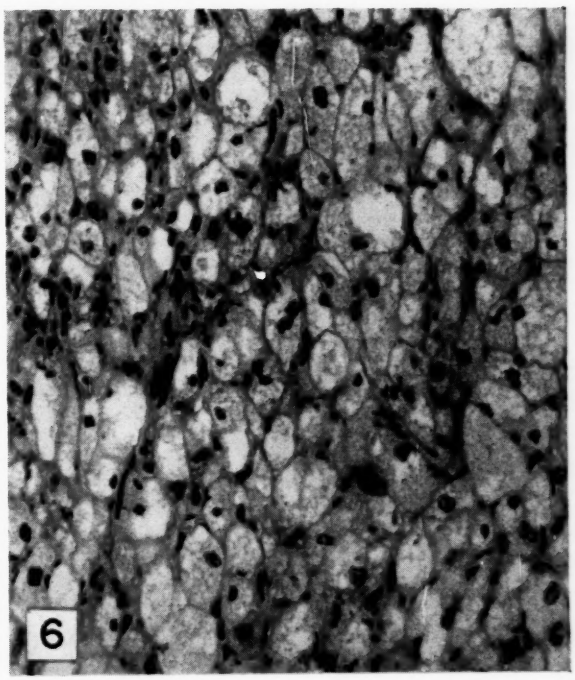


FIG. 3.—Section of R.B.–P.T.♯2820. Fibrosarcoma in an A × C control male. Mag. × 200.

FIG. 4.—Section of R.B.–P.T.♯2830. Fibrosarcoma in an A × C diabetic male. Mag. × 200.

FIG. 5.—Section of R.B.–P.T.♯2923. Rhabdomyosarcoma in an A × C alloxan-refractive male. Mag. × 200.

FIG. 6.—Section of R.B.–P.T.♯2921. Liposarcoma in a Marshall diabetic male. Mag. × 250.

with 0.2 cc. of a 1 per cent solution of benzpyrene in paraffin.

5. Benzpyrene-induced sarcoma was observed in 67 per cent of the diabetic, 97 per cent of the alloxan refractive, and 90 per cent of the control rats in an average latent period of 164± 4.4, 189± 4.6 and 184± 7.2 days, respectively.

6. These benzpyrene-induced sarcomas, included 115 fibrosarcomas, 6 rhabdomyosarcomas, 3 liposarcomas, 2 osteosarcomas and 4 unclassified tumors.

7. Among the diabetic rats that survived the minimum latent period of 80 days, 10, 69, and 100 per cent, respectively, of the 3 strains developed subcutaneous sarcoma. The reduced percentage of tumor deaths in 2 of the 3 strains resulted from early death rather than a reduced susceptibility to induced sarcoma.

The evidence from this experiment shows that the diabetic condition induced by alloxan shortened the life span of the affected individuals, thereby reducing both the percentage of rats surviving long enough to develop benzpyrene sarcomas and the average latent period of those which did, but did not prevent or delay the malignant process in the rats surviving to the average time of occurrence for these neoplasms.

REFERENCES

1. Bailey, C. C., Bailey, O. T., and Leech, R. S. Alloxan Diabetes with Complications. New England J. Med., **230**:533–536. 1944.
2. Duff, G. L., and Starr, H. Experimental Alloxan Diabetes in Hooded Rats. Proc. Soc. Exper. Biol. & Med., **57**:280–282. 1944.
3. Dunn, J. S., and McLetchie, N. G. B. Experimental Alloxan Diabetes in the Rat. Lancet **2**:384–387. 1943.
4. Dunning, W. F., Curtis, M. R., and Bullock, F. D. The Respective Roles of Heredity and Somatic Mutation in the Origin of Malignancy. Am. J. Cancer, **28**:681–712. 1936.
5. Dunning, W. F., Curtis, M. R., and Wood, F. C. Volume of Injection and Concentration of the Carcinogenic Chemical as Factors in the Initiation of the Malignant Process and Their Bearing on the Somatic Mutation Hypothesis. Am. J. Cancer, **39**: 70–93. 1940.
6. Goldfeder, A. Der Metabolismus von Kohlehydraten, Calcium und Jod bei experimentellen bösartigen Geschwülsten. Ztschr. J. Krebsforsch., **27**:503–536. 1928.
7. Gomori, G., and Goldner, M. G. Production of Diabetes Mellitus in Rats with Alloxan. Proc. Soc. Exper. Biol. and Med., **54**:287–290. 1943.
8. Joslin. E. P. The Diabetic Situation in Massachusetts. New England J. Med., **219**:547–555. 1938.
9. Kaplan, N. O., Franks, M., and Friedgood, C. E. Metabolism in Diabetic Coma Produced by Alloxan. Science, **102**:447–449. 1945.
10. Lynch, G. W. Diabetic Deaths in Boston During 1935. New England J. Med., **215**:822–826. 1936.
11. Robbins, S. L., and Tucker, A. W. The Cause of Death in Diabetes. A Report of 307 Autopsied Cases. New England J. Med., **231**:865–868. 1944.
12. Tannenbaum, A. The Dependence of Tumor Formation on the Degree of Calorie Restriction. Cancer Research, **5**:609–615. 1945.
13. Warren, S. Pathology of Diabetes Mellitus. Second edition. Philadelphia: Lea and Fibiger. 1938.
14. Young, N. F., Kensler, C. J., Seki, Louise, and Homburger, F. Deposition of Liver Glycogen in Normal Mice and in Mice Bearing Sarcoma 180. Proc. Soc. Exper. Biol. & Med., **66**:322–323. 1947.

Abstracts

Clinical and Pathological Reports

Clinical investigations are sometimes included under Reports of Research

Urinary System -- Male and Female

Renal Adenomas in Hypernephromatous Kidneys: A Study of their Incidence, Nature and Relationship. Cristol, D. S., McDonald, J. R., and Emmett, J. L. [Mayo Clin., Rochester, Minn.] *J. Urol.*, **55**:18-27. 1946.

A study of the gross and microscopic characteristics of 37 adenomas is utilized to interpret the pathogenesis, structure, classification and relationship of these lesions. Adenomas are seen to occur frequently in association with cysts, their incidence increasing with each succeeding decade past early middle life and somewhat approximating the age incidence of renal carcinoma. Adenomas are seen to occur more frequently in kidneys containing clinical cancer than in significant series of kidneys examined at necropsy. Reasons are presented for considering adenomas as malignant growths.—Authors' summary (W. F. W.)

Liposarcoma of Kidney: Report of a Case Presenting an Unusual Syndrome. Fish, G. W., and McLaughlin, W. L., [Columbia Univ., and Presbyterian Hosp., New York, N. Y.] *J. Urol.*, **55**:28-35. 1946.

A female of 28 with some of the features of the tuberous sclerosis complex was found to have a liposarcoma of the kidney.—W. F. W.

Mucinous Adenocarcinoma of the Pelvis of the Kidney. Ackerman, L. V. [Ellis Fischel State Cancer Hosp., Columbia, Mo.] *J. Urol.*, **55**:36-45. 1946.

Glandular type of metaplasia of the epithelium of the renal pelvis developing into a mucinous adenocarcinoma was found in a patient with kidney infection and stones. The changes evolved over a period of 14 years. Abnormal epithelium was implanted in the wound at the time when the local recurrence of a mucinous carcinoma appeared. Subsequent invasion into the peritoneal cavity with involvement of many organs occurred and death resulted in 6 months. The total course of the disease was 20 years. The unusual type of metaplasia has been reported once before, but this is the first instance of a mucinous carcinoma having its origin from kidney pelvis epithelium. —W. F. W.

Angioma of the Kidney. Hamm, F. C. [M. C., A. V. S.] *J. Urol.*, **55**:143-148. 1946.

The literature is reviewed and a case added.—W. F. W.

Wilm's Tumor in 75 Year Old Male: Report of a Case. Twinen, F. P. [James Buchanan Brady Foundation of N. Y. Hosp., New York, N. Y.] *J. Urol.*, **55**:246-251. 1946

A Wilms' tumor involving the entire kidney and ureter in a 75 year old man is reported.—W. F. W.

Hemanigiona of the Kidney: Report of an Additional Case. Dorman, H. N., and Fowler, H. A. *J. Urol.*, **55**:348-357. 1946.

The literature is reviewed and a case added, bringing the total number of reported cases to 54. Hematuria is the first and frequently the only symptom. Pain and urinary frequency due to passage of blood clots may be present. The diagnosis has been made by the pathologist rather than by the clinician in all cases except one. Angiomas probably explain many instances of essential hematuria. The lesions frequently occur on the renal papillae and may be so minute as to be missed unless macroscopic serial sections are made and every suspicious area examined microscopically. Profuse hemorrhage may result from a microscopic lesion of the kidney.—W. F. W.

Papilloma of an Ectopic Kidney. Case Report, and Review of Twenty-Two Tumors in Ectopic and Ptotic Kidneys. Gilbert, J. B. [Schenectady, N. Y.] *J. Urol.*, **55**:445-453. 1946.

The case presented is the first recorded instance of a papilloma arising in the pelvis of an ectopic kidney. Review of the literature revealed only 22 instances of tumors in abnormally placed kidneys, 5 involving ectopic and 17 in ptotic kidneys. An analysis of the cases is presented. —W. F. W.

The Prognosis and Problems in Renal Tumors. Deming, C. L. [Yale Univ., and New Haven Hosp., New Haven, Conn.] *J. Urol.*, **55**:571-582. 1946.

This report of 82 cases comprises a detailed study of renal tumor cases admitted to the New Haven Hospital during a 23 year period. Eleven tumors (13.4%) occurred during the first decade of life. Fifty-nine tumors (72%) were in males, 23 (28%) in females. In 53 cases the tumor was on the right side, in 29 cases on the left side. Classification is discussed briefly. The prognosis of malignant renal tumors is much more severe than is indicated by 5 year follow-up reports. In the present series 19.5% lived 5 years, 14.6% lived 10 years and 9.08% are alive without evidence of tumor. The problems are mani-

fold, embracing hereditary, congenital and acquired factors. Biological proof in addition to gross and microscopic examination for malignancy in a kidney tumor must be considered. Individual defense measures on the part of the host against the development of renal neoplasms are probably a natural response. It is doubtful whether the so-called controlled cases in this series had tumors which could withstand both the pathological and biological tests for malignancy. Their recovery can be explained in addition to surgery either on the basis of a non-malignant tumor as shown by biological tests, or on the basis of natural factors of defense. Since treatment by surgery and irradiation promises little, we can expect meager improvement in end results until some of these problems can be solved.—W. F. W.

Thrombosis of the Inferior Vena Cava Associated with Malignant Renal Tumors. NEY, C. [Montefiore Hosp., New York, N. Y.] *J. Urol.*, 55:583-590. 1946.

Ten cases of tumor thrombosis of the inferior vena cava associated with malignant renal tumors are added to the 41 previously described in the literature. An analysis of these cases indicates: (a) Renal tumors are by far the most common growths associated with tumor thrombosis of the inferior vena cava. (b) The thrombus is usually an extension from the renal vein (42 cases from a total of 51). (c) Most of the patients (35) have had the tumor in the right kidney, probably due to the short renal vein on the right. (d) Males predominate (42). (e) Many patients (20) have extension of the thrombus into the right auricle. (f) Edema of one or both lower extremeties is a common finding in these cases. (g) Direct invasion of the inferior vena cava is an important cause of thrombi. (h) The direction of the thrombus is not entirely controlled by the flow of blood. (i) Patients with tumor thrombosis of the inferior vena cava rarely live more than 6 months after signs of obstruction have occurred.—W. F. W.

Solitary Testicular Metastasis Simulating Primary Tumor and Antedating Clinical Hypernephroma of the Kidney: Report of a Case. BANDLER, C. G., and ROEN, P. R. [New York Post-Graduate Hosp., New York, N. Y.] *J. Urol.*, 55:663-669. 1946.

A rare case of testicular metastasis from hypernephroma of the kidney is presented. The testicular metastasis antedated the clinical detection of hypernephroma by 2 years. The patient remains well 3½ years following orchidectomy and 1 year following nephrectomy. The testicular tumor was erroneously believed to be a rare primary neoplasm in the 2 years preceding clinical recognition of the renal tumor. The presence of a solitary metastasis is no contraindication to surgery in hypernephroma. Metastasis in general is discussed.—W. F. W.

Lymphoblastoma of the Kidney. FREIFELD, S. E. [Univ. of Texas, Galveston, Texas] *Radiology*, 46:507-510. 1946.

A case is reported of generalized lymphosarcoma with infiltration of the kidneys in which the pyelograms resembled polycystic disease.—R. E. S.

Periarteritis Nodosum and Wilm's Tumor—Case Report. DAY, H. W., and HESSER, H. H. [Kansas City, Kans.] *J. Kansas M. Soc.*, 47:202-203. 1946.

Case report. The patient, an 11 year old boy, had survived the removal of a Wilm's tumor of the left kidney at the age of 3 months. His death was due to periarteritis nodosa; no evidence of recurrence of the previous tumor was found at autopsy.—E. B. B.

Serious Genito-Urinary Lesions Accompanied by Essentially Negative Urinary Findings. DUNCAN, I. G. [Univ. of Tennessee Coll. of Med., Memphis, Tenn.] *South. M. J.* 39:316-320. 1946.

A urinalysis may be unreliable as an indicator of far advanced pathological conditions of the urinary tract in many cases. The author cites these among others: (1) infections that do not communicate with the pelvis of the kidney as do perinephritic abscess or a carbuncle of the kidney; (2) tumors that do not bleed continuously; (3) noninfected hydronephrosis; and (4) stones or kinking of the ureter obstructing flow of urine from one side. Of the patients illustrating these points, one was a woman of 62 years who had pain in the right kidney with previous episodes of hematuria. Although the urine was normal at the time of examination, she had an advanced papillary carcinoma of the kidney. Another woman, 30 years old, discovered a large mass in the left upper quadrant of the abdomen during the fourth month of pregnancy. Urinalysis was negative, but during an exploratory laparotomy a large carcinoma of the kidney was found.—W. B. A.

Multiple Primary Carcinomas of the Kidney and Bladder. RAPPOPORT, A. E., NIXON, C. E., and SALMERI, E.J. [Fletcher Gen. Hosp., Cambridge, Ohio] *Am. J. Clin. Path.*, 16:341-346. 1946.

Case report.—S. H. D.

Infiltrating Carcinoma of the Bladder: Relation of Depth of Penetration of the Bladder Wall to Incidence of Local Extension and Metastases. JEWETT, H. J., and STRONG, G. H. [Johns Hopkins Hosp., Baltimore, Md.] *J. Urol.*, 55:366-372. 1946.

One hundred and seven autopsies showing infiltrating carcinoma of the bladder are reviewed, and the relation of the depth of penetration of the bladder wall to the incidence of metastases, lymphatic capillary invasion and perivesical fixation is noted. Designating each case with any of these evidences of tumor as inoperable, the potential curabilities were 100%, 86.6%, and 26% for tumors showing submucosal infiltration, muscular infiltration and perivesical infiltration, respectively. The cardinal sites of metastases were regional lymph nodes, liver, lungs and vertebral column, including sacrum and pelvis, in that order.—W. F. W.

Malacoplakia of the Bladder: Report of Two Interesting Cases. CRISTOL, D. S., and BRODERS, A. C. [Mayo Clin., Rochester, Minn.] *J. Urol.*, 55:260-266. 1946.

Two cases of malacoplakia of the bladder are presented

and the literature reviewed. The cause of the condition is unknown. Grossly, the lesions appear as grayish-yellow or yellow-brown, flat-surfaced plaques varying in number, size and distribution. They are occasionally raised 1 to 2 mm. above the level of the mucosa and have abrupt or slightly overhanging edges. A zone of hyperemia frequently surrounds the lesions. The centers of the large plaques often appear umbilicated and may be ulcerated. Histologically the principal cellular elements are large oval or polyhedral cells, frequently closely aggregated and found in the submucosa. The majority of patients are women past 30 years who have had repeated episodes of cystitis. All age extremes have been reported in both sexes. Urinary frequency and hematuria are the prominent symptoms. Treatment is not standardized but fairly good results have followed fulguration.—W. F. W.

Open X-Ray Therapy in Carcinoma of the Bladder. Rose, D. K. [Washington Univ. Sch. of Med., Mallinckrodt Radiological Inst., and Barnes Hosp., St. Louis, Mo.] *J. Urol.*, **55**:267-272. 1946.

A technic for the direct and open radiation of invasive bladder carcinoma is described. It is suggested only in the most desperate types of bladder tumor. The author admits that the small number of treated cases and the short follow up periods do not permit any final evaluation of the method, but believes the procedure worthy of consideration in certain bladder carcinomas.—W. F. W.

Endometriosis of the Urinary Bladder with Report of a Case. Ockuly, E. A., and Helwig, F. C., [Hqs. AAF Regional and Convalescent Hosp., Coral Gables, Fla.] *J. Urol.*, **55**:464-469. 1946.

A case is reported and the histopathology discussed. The importance of a painstaking history and of accurate interpretation of the cystoscopic findings is emphasized. In the entire series of 46 cases of ectopic endometriosis of the bladder reported in the literature, the correct diagnosis was made only twice from biopsy studies. This low figure may be due in part to inadequate removal of tissue.—W. F. W.

Treatment of Carcinoma of the Bladder for the Past Five Years with Special Reference to the Closed Method of Treatment. Milner, W. A. [Albany Med. Sch., and Albany Hosp., Albany, N. Y.] *J. Urol.*, **55**:607-612. 1946.

Two hundred and forty-five patients with carcinoma of the bladder, operated on during the years from July 1, 1940 to July 1, 1945, form the basis for this report. Accurate follow-up records exist for 188 (76.7%), but for 57 (23.3%) they are incomplete. The average age was 62.9 years. Sixty-five (26.8%) were females; 180 (73.2%) were males. An average of 12½ months elapsed between the first symptoms and the actual diagnosis. Hematuria was the outstanding or initial symptom in 230 cases (94%), and 229 patients (93%) were treated by transurethral resection. Along with this, radon seed implantation and deep x-ray therapy were used in certain cases. Cases are selected for radium implantation on the basis of evidence of infiltration seen at preliminary cystoscopy. Deep x-ray therapy is employed only in those showing infiltration where something in the way of extra help is felt necessary. Segmental resection was done 15 times. Total cystectomy with uretero-sigmoidal transplantation was done 3 times. The pathology is briefly summarized. The operative mortality for total cystectomy was 33.3%, for segmental resection 6.6%, and for transurethral resection 0.44%. Of the 189 cases on whom definite information is available 37.5% are known dead from all causes, whereas 32.2% died as a result of their disease. The results of treatment are tabulated and the author concludes that transurethral resection with or without radon seed implantation, as the case requires, offers an excellent chance for cure in the less invasive types of bladder tumors.

Transurethral operation to be properly effective must remove all or as much as possible of the tumor tissue without danger to the patient and must include thorough fulguration of the base of the tumor. This method of approach gives a great many cures without the attendant morbidity of cystotomy. In the incurable type of tumor, it offers palliation without the discomfort, both mental and physical, which attends permanent cystotomy. More radical segmental resections and an increased number of total cystectomies will give a higher percentage of cures in the more invasive types of malignant bladder tumors. —W. F. W.

Infiltrating Carcinoma of the Urinary Bladder: Diagnosis and Clinical Evaluation of Curability. Jewett, H. J., and Strong, G. H. [Johns Hopkins Hosp., Baltimore, Md.] *South. M. J.*, **39**:203-207. 1946.

One hundred and seven cases of infiltrating carcinomas of the bladder studied at autopsy are divided into 3 groups: (1) those in which penetration was limited to the submucosa, (2) those in which penetration extended into the muscularis, and (3) those in which perivesical infiltration was present. The potential curability in each group was determined by the presence of regional or distant metastases, perivesical capillary lymphatic invasion only, or perivesical fixation of the mass. In the first group, potential curability was 100%, in the second group 86.6% and in the third only 26%. Eighty-nine of the cases fell in the third group. The diagnosis of a tumor which has invaded the perivesical tissues can be made in a high percentage of cases in the male by recto-abdominal palpation under anesthesia. Recognition of the extent of infiltration preoperatively aids in the selection of the most efficacious therapeutic procedure.—W. A. B.

Myxomatous Tumor of the Bladder Simulating Stone in the Bladder, in a Child aged 5 Years. Meade, H., *Brit. J. Urol.*, **15**:10-11. 1943.

A boy aged 5 had, projecting into the bladder, a polypoid tumor composed of myxomatous fibrous tissue covered by transitional epithelium without any evidence of malignancy.—E. L. K.

[Papillary Carcinoma of Right Ureter.] Case Records of the Massachusetts Gen. Hosp. Case 32361. *New England J. Med.*, **235**:337-340. 1946.

A discussion is presented of a case treated by surgery. —M. H. P.

Primary Melano-Epithelioma of Female Urethra: Review of Literature; Report of Three Cases. LONG, G. C., COUNSELLER, V. S., and DOCKERTY, M. B. [Mayo Clin., Rochester, Minn.] *J. Urol.*, **55**:520-529. 1946.

Primary melano-epithelioma of the female urethra is an extremely rare disease (1 in 230,000 females). Three cases encountered at the Mayo Clinic in the last 37 years are reported, making a total of 14 cases described in the literature in approximately 50 years. It is a disease of the aged. As is true of this lesion in other locations, the prognosis is poor. The most common symptoms are a serosanguineous vaginal discharge and a dark-colored tumor. Treatment by electrocautery excision supplemented with roentgen and radium therapy has not been very effective.—W. F. W.

Papillomata of the Urethra. RICHES, E. W. [Middlesex Hosp., London, England] *Brit. J. Urol.*, **16**:12-15. 1944.

These tumors are either (a) villous growths resembling papilloma of the bladder, found most often in the posterior urethra and covered with transitional epithelium, or (b) sessile warts of the anterior urethra covered by squamous epithelium. Three examples of each type are described. —E. L. K.

ORAL CAVITY AND UPPER RESPIRATORY TRACT

Peroral Endoscopy. CLERF, L. H., FOX, J. R., and FIELDS, J. A. [Philadelphia, Pa.] *Arch. Otolaryng.*, **44**: 337-367. 1946.

A conclusive diagnosis of laryngeal papilloma in children and primary carcinoma of the trachea can only be made by direct examination and biopsy. Repeated endolaryngeal excision is the treatment of choice for a papilloma. Fisher recommends electrocoagulation of the carcinoma of the trachea through a bronchoscope with the tumor under direct vision and such treatment should be followed by irradiation with roentgen rays. A more general use of the bronchoscope in patients with unexplained hemoptysis would probably reveal a larger number of rare osteomas of the trachea. Some recent literature of adenomas of the bronchus is reviewed with no definite conclusions. The greatest problem in successfully treating carcinoma of the bronchus is the inability to make a diagnosis sufficiently early. The greatest value of irradiation therapy of these tumors is in its palliative effect. A bronchoscopic examination is of limited value for mediastinal tumors. The diagnosis of benign tumors of the esophagus cannot always be made by esophagoscopic examination. Difficulty is encountered in the esophagoscopic differentiation between intramural and extramural tumors and the extraesophageal tumors pressing and deforming the esophagus. To eliminate blind spots, gastroscopic procedures on patients in the sitting posture is preferable for the study of cancer in the upper third of the stomach.—C. R. N.

Fréquence de l'envahissement lymphatique révélé par l'évidement sous-maxillaire dans le cancer de la lèvre inferieure. (Statistique du Centre anticancereux de Toulouse (1929-1942). [Frequency of Lymphatic Involvement Revealed by the Removal of the Submaxillary Ganglionic Chain in the Cancer of the Lower Lip. (Statistics of the Toulouse Anticancer Center (1929-1942).] DUCUING, J., and NÈGRE, *Bull. Assoc. franç. p. l'étude du cancer*, **31**:11-12. 1943.

Of 119 patients who have been followed, 57 (47.9%) gave evidence of neoplastic involvement of the lymph nodes, and 62 (52.1%) had no evidence of ganglion involvement.—R. J.

Malignant Granuloma of the Nose. HARGROVE, S. W. G., FODDEN, J. H., and RHODES, A. J. [Roy. Salop Infirmary, Shrewsbury, England] *Lancet*, **2**:596-599. 1946.

A full description of a case plus photomicrographs is given. The possible neoplastic nature of the affection is discussed.—E. L. K.

Odontogenic Tumors. A Classification Based on Observations of the Epithelial, Mesenchymal, and Mixed Varieties. THOMA, K. H., and GOLDMAN, H. M. [Army Inst. of Path., Washington, D. C., and Harvard Sch. of Dental Med., Boston, Mass.] *Am. J. Path.*, **22**:433-471. 1946.

The odontogenic tumors are classified into three groups: epithelial, mesenchymal, and mixed. The dentinoma, a pure mesenchymal tumor, is composed of connective tissue in which denticles or islands of irregularly formed dentin are present. The odontogenic mixed tumors consist of epithelial and mesodermal elements which are in combination in various proportions and arrangements. Three types are recognized: soft, soft and calcified, and calcified. The soft type has been differentiated from the solid adamantoblastoma.

There is evidence of the inductive influences of one tissue on another in the odontogenic mixed tumors. It is noted that epithelium in these tumors seems to stimulate dentin formation, but that the presence of epithelium is not necessary for the production of dentin. Also, dentin is formed in the presence of epithelial cells not differentiated into ameloblasts. Neoplastic adamantine tissue and enamel-forming ameloblasts have been distinguished. The presence of these two types accounts, in part, for the formation of the soft and calcified odontogenic mixed tumors.—Author's summary. (J. G. K.)

Odontoma of the Nasopharynx. MCCLURE, G. [Oakland, Calif.] *Arch. Otolaryng.*, **44**:51-60. 1946.

Case report of a compound composite odontoma (osteofibroma of dentigerous origin) of the nasopharynx is given.—C. R. N.

Obstruction of the Nasopharynx Secondary to Choanal Polyp of Antral Origin. Report of Three Cases. MYERS, D. [M. C., A. U. S.] *Arch. Otolaryng.*, **44**:328-333. 1946.

Description of 3 cases of choanal polyps which were removed surgically by the Caldwell-Luc operation.—C. R. N.

Otolaryngology. FLAKE, C. G. [Children's Hosp., Peter Bent Brigham Hosp., and Harvard Med. Sch., Boston, Mass.] *New England J. Med.*, **235**:684-691. 1946.

Cancer and hemangioma of the larynx are among the subjects discussed in this review of 1945 literature on otolaryngology.—M. H. P.

Leiomyoma of the Larynx. NEIVERT, H., and ROYER, L. [Columbia Presbyterian Med. Center, New York, N. Y.] *Arch. Otolaryng.*, **44**:214-218. 1946.

First true leiomyoma of the upper part of the larynx in the American literature is reported. Tumor was removed and recovery was uneventful.—C. R. N.

Sarcoma of the Larynx. Report of Eight Cases. CLERF, L. [Philadelphia, Pa.] *Arch. Otolaryng.*, **44**:517-524. 1946.

On the basis of 8 reported cases, plus other personal experiences, the author concludes that fibrosarcoma of the larynx should be treated surgically and that complete removal is necessary. The majority of these tumors can be removed without sacrifice of the larynx. Although sarcoma of larynx is rare it should be considered as a possible diagnosis.—C. R. N.

INTRATHORACIC TUMORS

Primary Bronchogenic Carcinoma. A Report of 47 Cases. CORSELLO, J. N., and O'BRIEN, W. B. [Providence and Wallum Lake, R. I.] *Rhode Island M. J.*, **30**:15-20. 1947.

Observations on 47 cases of primary bronchogenic carcinoma reveal 41 were males, 6 were females and 91% were between 40 and 69 years of age. The average duration of life for 38 of the known dead from the onset of symptoms to fatal termination was 17.3 months. A majority of patients sought medical care immediately after the onset of symptoms or soon afterwards yet there was an average time lapse of 8.2 months between the patient's first visit to a doctor and the correct diagnosis. The authors believe that many patients with primary bronchogenic carcinoma are already beyond the curable stage by the time the initial symptoms appear. It is urged that efforts be directed toward discovery of the disease while it is still in a preclinical stage by utilizing the tuberculosis case-finding technics and by routine annual chest x-rays of all persons over 40.—M. E. H.

Hypertrophic Secondary Pulmonary Osteoarthropathy (Marie's Syndrome). DUNCAN, J. H. [Sault Ste. Marie, Ont.] *Canad. M. A. J.*, **56**:70-71. 1947.

Case report. Postmortem examination showed a chronic bilateral adhesive pleurisy and a large papillary adenocarcinoma of the left lung which microscopically resembled prostate tissue.—M. E. H.

Resectable Pulmonary Lesions. RUMEL, W. R. [Univ. Of Utah Med. Sch., Salt Lake City, Utah] *Rocky Mountain*, M. J., **43**:989-1001. 1946.

The operative mortality rate associated with resection of lung tissue has been reduced to such a point that no hesitancy should be felt in recommending this form of treatment. The more common resectable pulmonary lesions are presented and diagnosis discussed. Figures presented from a study of the literature revealed 93.7% of 443 collected cases of primary lung tumors were malignant and 6.3% benign. Carcinoma occurred in 407 and sarcoma in 8 of the malignant cases. Among the 28 benign lesions, 23 were bronchial adenomas, and one each of hematoma, fibroma, myxochondroma, teratoma and neurofibroma.—M. E. H.

Clinical Pathological Conference. LUND, P. K., Editor [Seattle, Wash.] *West. J. Surg.*, **54**:365-368. 1946.

The clinical diagnosis was malignant adenoma of the bronchus; the pathological study favored a diagnosis of malignant mixed tumor of the right lower lobe of the lung with invasion of hilar lymph nodes, mediastinum and inferior vena cava.—M. E. H.

Tumors of the Lung. CLAGETT, O. T. [Mayo Clinic, Rochester, Minn.] *South. M. J.*, **39**:138-143. 1946.

Discussion of the problem.—W. A. B.

Spontaneous Regression of Metastatic Sarcoma. Report of a Case. ROSENMAN, R. H. [Wayne County Gen. Hosp., Eloise, Mich.] *Am. J. Clin. Path.*, **16**:281-289. 1946.

Reports are given of fibrosis in the pulmonary parenchyma diagnosed roentgenologically as metastases of an osteogenic chondrosarcoma of the tibia.—S. H. D.

Clinic on Pneumonectomy, Stressing the Technic of Operation. BETTMAN, R. B. [Univ. of Illinois Coll. of Med., Chicago, Ill.] *S. Clin. North America*, **26**:143-151. 1946.

The technic of this operation upon which the cure for lung cancer often depends is described in detail.—J. L. M.

Surgery of the Mediastinum. ADAMS, W. E. [Univ. of Chicago Med. Sch., Chicago, Ill.] *S. Clin. North America*, **26**:130-142. 1946.

Included in this paper are case reports of a neurogenic tumor of the mediastinum, and of a carcinoma of the esophagus. Operative technic is diagramatically presented.—J. L. M.

HEART

Primary Tumor of the Heart Containing Epithelium-Like Elements. ANDERSON, W. A. D., and DMYTRYK, E. T. [St. Louis Univ. Sch. of Med., St. Louis, Mo.] *Am. J. Path.*, **22**:337-349. 1946.

A case report. The authors conclude that the tumor arose from pericardial elements included in the atrial wall during cardiac development.—J. G. K.

GASTROINTESTINAL TRACT

Diagnostic and Therapeutic Considerations of Gastrointestinal Bleeding. JONES, C. M. [Harvard Med. Sch.,

and Massachusetts General Hosp., Boston, Mass.] *New England J. Med.*, **235**:773-776. 1946.

A general discussion concerning bleeding from the esophagus, stomach, and intestine, as caused by various types of lesions including tumors. Physicians are warned that obvious sources of bleeding may not provide a true explanation for hemorrhagic episodes; *e.g.*, hemorrhoids or anal fissures may be incorrectly accepted as the cause of rectal bleeding actually due to carcinoma. Thorough diagnostic measures, postponed in part until after the hemorrhage, are urged. Cancer should always be suspected in the presene of colonic bleeding. Gastroduodenal hemorrhage is usually due to peptic ulcer, but sometimes also can be caused by cancer of the stomach, and by carcinoma or leiomyosarcoma of the duodenum. Esophageal bleeding is due either to varices or cancer in most cases.—M. H. P.

Roentgenologic Examination in Patients with Bleeding from the Gastrointestinal Tract. SCHATZKI, R. [Harvard Med. Sch., and Massachusetts Gen. Hosp., Boston, Mass.] *New England J. Med.*, **235**:783-786. 1946.

A general discussion of the use of x-ray for differential diagnosis in patients with gastrointestinal bleeding is given. It is no longer believed necessary to postpone roentgenography for 2 weeks or more after hemorrhage; the author has examined patients even during bleeding, although not during shock. Fluoroscopy and a single spot film may be sufficient to demonstrate a large cancer. However, blood clots may produce a picture similar to polypoid tumors, and questionable cases should be excluded by re-examination. Repeated hemorrhage without other clinical symptoms is often found in gastric leiomyomas, fibromas, neurofibromas, and their malignant variants, with similar and characteristic x-ray appearance. Examination should not stop at the duodenal cap, but should be continued even if only one source of bleeding has been found. The author reports finding a bleeding fibrosarcoma in the third portion of the duodenum in a patient who had a large duodenal ulcer that at first was considered sufficient to explain the hemorrhage.—M. H. P.

Dyspepsia, Ulcer and Gastric Cancer. ANGLEM, T. J. [Boston Univ. Sch. of Med., Boston, Mass.] *New England J. Med.*, **235**:322-325. 1946.

Physicians are blamed for much of the long delay commonly noted in gastric cancer cases before diagnosis is established. An analysis of the records of 188 cases of this disease reveals that 70% were hopeless when first seen by the surgeon; in 127 cases the patient was responsible for an average delay of 9 months, and in 72 cases the blame for an average delay of 17 months rested on the physician. Epigastric pain or burning, epigastric distress or fullness, and indigestion were the first symptoms in 70% of the patients. In persons over 45 years old, these symptoms should not be treated casually, but should provoke a searching investigation for cancer. X-ray examinations should be repeated at short intervals if the symptoms persist; in the present series, the first x-ray examination failed to establish the diagnosis in 24% of the cases. Where a diagnosis of gastric ulcer has been made, the chance of malignancy may be 10-14%, and patients should be given the benefit of surgery if possible rather than medical therapy. A therapeutic trial of medical treatment is especially condemned for differential diagnosis between ulcer and cancer.—M. H. P.

Extramedullary Plasma Cell Tumor of Stomach: A Case Report. COURET J. S. [Hotel Dieu, New Orleans, La.] *Am. J. Clin. Path.*, **16**:213-218. 1946.

Case report.—S. H. D.

Roentgen Demonstration of a Benign Intramural Tumor (Fibromyoma) on the Greater Curvature of the Stomach. LEWITAN, A., and NYGAARD, K. K., [Brooklyn, and White Plains, N. Y.] *Radiology*, **46**:590-593. 1946.

Case report.—R. E. S.

Surgical Treatment of Malignant Tumors of the Duodenum Exclusive of Those Arising from the Papilla of Vater. BRUNSCHWIG, A., and TIHOLIZ, I. C. [Univ. Chicago Sch. of Med., Chicago Ill.] *S. Clin. North America*, **26**:163-175. 1946.

Results of surgical treatment in 5 cases of malignant tumors of the duodenum are described. The tumors include carcinomas of the first, second and third segments, spindle cell sarcoma of the third segment, and round cell sarcoma involving most of the duodenum. The operations are described in detail.

General conclusions are not yet possible in regard to the surgery of primary malignant neoplasms of the duodenum. Pancreatoduodenectomy is the most radical procedure, but good results have been achieved with more conservative procedures. The authors stress that as in any surgical attack upon neoplasms, each patient presents individual problems which must be evaluated if the surgeon is to carry out the best operation for that patient —J. L. M.

Submucous Lipoma of the Jejunum: Report of a Case. CAVANAUGH, J. W., and MILLS, W. M. [Fort Dodge, Ia., and Topeka, Kans.] *J. Kansas M. Soc.*, **17**:51-52. 1946.

According to the operative records of the Mayo Clinic, benign neoplasms of the intestine are uncommon, their frequency being about one-half that of carcinoma. Yet at necropsy they have been observed twice as frequently. The most common are adenomas and myomas, with other forms occurring less often. The case reported is of a submucous lipoma of the upper jejunum causing intestinal obstruction in a 55 year old woman.—E. B. B.

Primary Carcinoma of the Ileum (Case Report). LEOPARD, J. M. [Univ. of Kansas Sch. of Med., Kansas City, Kans.] *J. Kansas M. Soc.*, **17**:49-51. 1946.

Primary carcinoma of the small intestine comprises a small percentage of the neoplasms of the gastrointestinal tract, and is rarely recognized preoperatively. It may occur as any one of the following types: single or multiple polyp that has undergone malignant degeneration; annu-

lar constriction lesion; or carcinoid or argentaffine tumor. A case is presented of a 61 year old white female who had a carcinoma of the small intestine with metastasis in the regional lymph nodes. The epithelium was suggestive of gastric rather than intestinal mucosa, and it was thought that this tumor may have originated in a Meckel's diverticulum.—E. B. B.

Multiple Carcinoid Tumours of the Bowl: Report of a Case. LYALL, A. [Royal Infirmary, Greenock, Scotland] *Glasgow M. J.*, **27**:300-306. 1946.

At autopsy on a 63 year old male, 7 tumors in the ileum and 1 in the ascending colon were found; the last-named had formed a metastasis in a lymph gland. The nature of carcinoid tumors and the origin of the Kulchitsky cell are discussed.—E. L. K.

Iron Deficiency and Anemia Associated with Carcinoma of the Proximal Portion of the Colon. CLARK, R. L., JR., POWER, M. H., HECK, F. J. and DIXON, C. F. [Mayo Clinic, Rochester, Minn.] *M. Clin. North America*, **29**: 958-972. 1945.

The studies reported were made on 23 patients with carcinoma in some portion of the colon. The age variation (38 to 72) of the 21 patients who had carcinoma of the proximal portion of the colon and the sex (10 women and 11 men) appeared to have no bearing on the degree or frequency of anemia.

The type of anemia that occurs with cancer of the proximal portion of the colon was observed to be the same as that produced by a deficient supply of iron for elaboration of hemoglobin. The abnormal demands made upon the iron supply of the body were noted to be increased in instances where the growth was situated in the proximal segment, and the absorption of dietary iron appeared to be more retarded than it was when the growth was situated in the distal portion of the colon. In all cases of cancer of the right half of the colon the concentration of serum iron was low. If severe anemia was present, a marked decrease in the concentration of serum iron was observed. The anemia could apparently be arrested, with the cancer *in situ*, following iron therapy if the iron was of sufficient amount and was absorbed. Recovery from the anemia following removal of the cancer was demonstrated to be dependent upon adequate absorption of iron. Administration and adsorption of iron following resection of the involved segment of colon resulted in a return of a normal concentration of serum iron and hemoglobin. Anemia accompanying carcinoma of the distal portion of the colon has been observed in 2 instances to be similar to that observed in conjunction with carcinoma of the proximal portion of the colon.—J. L. M.

Primary Resection of the Colon with Specific Reference to Surgical Diagnosis and Management. MEYER, K. A., and KOZOLL, D. D. [Cook County Hosp., Chicago, Ill.] *S. Clin. North America*, **26**:176-199. 1946.

A plan of management of lesions of the colon is presented which emphasizes an orderly sequence of events in diagnosis, standardized preoperative and postoperative regimen and an operative technic, which has resulted in a mortality rate of 4% and a minimal morbidity rate. Five case histories are presented. Preoperative and postoperative instructions are given in detail.—J. L. M.

Carcinoma of the Colon. LYALL, A. [Greenock Roy. Infirmary, Greenock, Scotland] *Glasgow M. J.*, **27**:29-44. 1946.

A description of an operation which the author has performed in 21 consecutive cases without mortality.—E. L. K.

Primary and Secondary Metastases from Cancer of the Colon and Rectum. DANIEL, W. H. [Los Angeles, Calif.] *South. M. J.*, **39**:480-482. 1946.

This is a resume of 978 cancers of the colon and rectum examined and treated by the writer. Of these, 286 were removed by radical surgical procedures. There were 108 primary metastases in this group. (Primary metastases are defined as those that are discovered at operation or on examination of the removed specimen; and secondary metastases, those that appear at a later date). In the remainder of the 978 which were inoperable there were 189 primary metastases. Secondary metastases occurred in 5 years in 65 cases which had been subjected to operation. The greatest number of secondary metastases occurred in the age group between the 40th and 49th year. Metastases in the operative wound occurred in 22 cases.—W. A. B.

A Resumé of the Management of Cancer of the Rectum and Colon. HAYES, H. T., and BURR, H. B. [Houston, Tex.] *South. M. J.*, **39**:435-439. 1946.

General discussion.—W. A. B.

LIVER

A Papillary Cystadenoma of the Common Hepatic Duct. ROGERS, K. E. [St. Michael's Hosp., Toronto, Ont.,] *Canad. M. A. J.*, **55**:597-599. 1946.

Benign tumors of the gall bladder or bile ducts are rare. In the case reported, the tumor on excision proved to be a benign papilloma. There was local recurrence in less than a year. The disturbance of liver function caused by its presence resulted in a fatal termination.—M. E. H.

[Colloid Carcinoma of Gall Bladder with Widespread Metastases.] Case Records of the Massachusetts Gen. Hosp. Case 32451. *New England J. Med.*, **235**:691-693. 1946.

A report of a case, in a man who also had epidermoid carcinoma of the bladder with cervical metastases, adenocarcinoma of the rectum and prostate, and biliary cirrhosis of the liver.—M. H. P.

Metastatic Cancer of the Extrahepatic Bile Ducts Producing Jaundice. HERBUT, P. A., and WATSON, J. S. [Jefferson Med. Coll. Hosp., Philadelphia, Pa.] *Am. J. Clin. Path.*, **16**:365-372. 1946.

Three cases are presented including 2 patients with carcinoma of the colon and 1 with lymphosarcoma.—S. H. D.